CORNELL CONFERENCES
ON THERAPY



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CORNELL CONFERENCES ON THERAPY

VOLUME FOUR

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It is never too late to give up our prejudices. No way of thinking or doing, however ancient, can be trusted without proof.

HENRY DAVID THOREAU

In ward and clinic the student is often told to do what in pharmacology he has been taught to avoid, and, conversely, in pharmacology he often learns to expect what turns out to be alien to the experience of the clinic It is quite clear that neither has taken full advantage of the opportunities afforded by the other It is also clear that there is urgent need for a forum where pharmacologists and clinicians may come together and talk these things over That, in essence, is the purpose of the Conferences on Therapy

The Cornell Conferences on Therapy were inaugurated in 1937 as a joint venture of the Departments of Medicine and of Pharmacology Arrangements were made for the participation of every department of Cornell University Medical College–New York Hospital and the collaboration of other institutions They are scheduled weekly throughout the larger part of the school year It is the policy to begin on time and end promptly at the end of an hour

There is considerable latitude in the conduct of the conferences Certain features characterize the majority of them A group of drugs, a therapeutic procedure, a symptom, or disease is selected as the topic for discussion Practical procedures for the use of the therapeutic measures are outlined by a clinician and, where feasible, a résumé of the experimental basis is presented by someone trained in the more basic sciences of physiology, pharmacology, or chemistry Approximately half of the period is devoted to informal discussion in which the audience is encouraged to take an active part

Free use has been made of the question as an especially effective device for exciting interest and focusing attention In some conferences the method of the round table discussion is employed, the questions being directed to a group of experts on the subject The most successful conferences are among those in which the largest part of the session is devoted to informal discussion through the medium of questions and answers Those, in which sharp differences of views develop and the evidence is probed, acquire a particularly stirring and

stimulating quality Therapeutic prejudice and vague opinion have a somewhat difficult time of it in these conferences

The scope covers the whole range of therapeutics To qualify for a conference, a subject must be a problem in therapy It may be old or new It should be important If there are widely divergent views concerning it, so much the better, since it is the function of the conference to point out how the evidence stands The order of subjects doesn't matter A series of conferences in a particular field has been attempted from time to time, as one series on the treatment of the blood diseases On the whole, it has seemed more practical to avoid the series on any one subject, and to take up such topics as seem feasible in relation to their interest at the time and the personnel available to lead the discussion

While the introductory remarks are often prepared, the discussion is for the most part unrehearsed and extemporaneous In many cases the chairman tries to lead the discussion into a planned direction, but frequently the course is determined by the nature of the questions in which the audience appears to show the greatest interest

The conference is no substitute for the formal lecture, the scientific article, or the textbook It is not a substitute for any traditional form of medical teaching It does not aim to treat any subject exhaustively, but only to explore some aspects of special interest, to analyze the evidence on controversial points of opinion and practice, to elaborate the physiologic, pharmacologic, and chemical basis of therapeutic measures, and to present these on the level of the general practitioner

There has been a good deal of experimentation in policy and technics Certain features have survived The purpose—to stimulate interest in rational therapy, the method—spontaneous, informal, and free discussion

The conferences were originally designed for the students of the third and fourth year classes of the medical college It was soon discovered that members of the house staff, of the attending staff, and visiting practitioners had an interest in

them After the first year's experience, it seemed that a permanent record would enhance their value Accordingly, they were taken down by a stenotypist in attendance at each session The success of the edited record led to the next step, the introduction of the conference to a wider audience through their monthly publication in the *Journal of the American Medical Association* from 1937 to 1940 In 1940 this system was transferred to the *New York State Journal of Medicine* A new monthly publication whose policy is to make more accessible to the general practitioner the specialized fields of clinical science, the *American Journal of Medicine*, expressed an interest in printing the edited record of some of these conferences Accordingly, the monthly publication system was revised, and since 1946 the plan was adopted to print one conference every other month in the *New York State Journal of Medicine*, and one every other month in the *American Journal of Medicine*

Through their publication it was hoped that they might serve to demonstrate some of the advantages of this method of learning and lead to its adoption by other institutions It is a method which can be readily adapted to the needs and means of small medical communities and hospital groups

There has been widespread interest in the publication of these conferences From the large volume of correspondence and the nature of the comments, it has become clear that they are filling a need in medical education Busy physicians find them a rich source of authoritative information in therapeutics, made more practical by the exchange of views among specialists and general practitioners, made more accessible by the restriction of their scope and the easy stirring style of the conference method

In response to numerous requests, the final step in their evolution was taken, namely, the annual publication of a volume representing a group of conferences selected in the main for their quality and enduring value

THE EDITORS

Preface to Volume IV

The selected conferences in this volume bring to 61 the total number published in the first four volumes of the *Cornell Conferences on Therapy* These represent the active participation of more than 100 individuals some having taken part in the conferences of all four volumes The principles governing the conduct of these weekly discussions of treatment have remained unchanged, but use has been made of the enlarged experience in the editing of the stenotyped records, with the view toward maintaining the facile style and clarity of text Every endeavor has been made to reduce questions to the most concise formulation, and no effort has been spared in revision to ensure that answers to them are direct and leave no doubt of their meaning

The original plan to discuss such aspects of a topic as may be of special interest at the time rather than attempt to exhaust a subject, is well illustrated in the current volume It contains two conferences on syphilis although one on syphilis appeared in Volume II A conference on the treatment of genitourinary infections and one on the treatment of painful disorders of skeletal muscle are included, although titles suggesting similar material were presented in Volume III The same subject is a new conference when new speakers are involved, new aspects considered and new viewpoints explored

As in the previous volumes a topic of general interest heads the list of conferences In the current volume, the leading topic on Household Poisonings is not only of importance to physicians but one which should prove useful reading for the housewife and those especially preoccupied with common hazards in the home

In the Preface to Volume II, attention was called to the wide range of readers for whom the selection of conferences was designed the general practitioner, the specialist, the teacher, the intern, the medical student, the pharmacist, and the nurse' Two other uses have since come to our notice An example of one was the use of a conference as an item in the revision of th *U S Pharmacopoeia* In a conference entitled ' The Dose of a Drug," which headed the list in Volume III, the point was developed that the term "average dose as commonly employed represented a misconception in the light of present knowledge The arguments were carried to the Revision Committee of the *U S Pharmacopoeia,* and the discussions which ensued resulted in replacing ' average dose" which had appeared in the *Pharmacopoeia* since 1820 by "usual dose' in the latest revision, U S P XIV An example of the second was the use of a conference as a stimulus to research In one conference, penetrating questions raised by members of the audience aroused interest in the need for more knowledge and provided a stimulus for a new investigation on the subject of discussion, since no satisfactory answer could be supplied

Conviction is steadily growing that the main source of strength of these conferences lies in the policy of maintaining the discussions on a high level of free exchange of thought with emphasis on the defense of points of view that speakers present The understanding of this purpose and the generous cooperation of the clinicians and other scientists who have participated in the discussions have gone a long way in eliminating from these conferences the four causes of error so aptly set forth by the Anglican scientist of the thirteenth century, Br Roger Bacon

1 Unworthy authority
2 Custom
3 Opinion of the unskilled
4 Concealment of ignorance with the pretense of knowledge

THE EDITORS

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They are indebted to the collaborators who assisted in the editing of the original stenotyped notes to Miss Lori Beller for checking the intermediary drafts of stenograms to Miss Muriel Alice Gold whose reading of proof eliminated several errors that had been overlooked and to Miss Ida Dailes for unusually careful reading of galley and page proof They are especially indebted to Dr Theodore Greiner for the reading of proof and other valuable aids in the final preparation of Volume IV

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Household Poisonings, I

Dr. Harry Gold: The conference today is on the subject of household poisons. It is not very easy to draw a line around the group of household poisons. It seems to include many of the poisons used in industry, many of the medicines found in drugstores, and chemicals found in grocery stores, paint stores, and others. I suppose that the best we can do is consider a few of the more common ones and perhaps some of the more interesting poisons.

Any one physician may not see a great many cases of poisoning in the home, but in the aggregate the number of cases is very large. In one report, made in 1934 by Aikman of Rochester, attention was called to the fact that 1 per cent of all the children in the Strong Memorial Hospital were admitted for some form of poisoning. About one-quarter of all those cases were accidental poisonings and about one half of the cases were therapeutic poisonings. That one of every hundred children in a hospital was there because of poisoning indicates that the topic of the conference today is of major importance. Perhaps in the course of the discussion we may learn how these matters stand in the New York Hospital.

The major proportion of household poisonings occur in children. There is a report to the effect that, in 1929, there were in the United States 530 deaths due to accidental poisoning in children under five. The numbers declined all the way down to 50 cases during the next 5 year age period. It seems that in the age group up to five, there is a population

ceived the equivalent of about 12 grains (0 8 Gm) of Amytal for an adult. Such a dose is not likely to prove fatal but produces a fairly high degree of depression in a great many The dose of the atropine presents a point of interest It is commonly stated that the fatal dose of atropine for children is about 10 mg, and for adults, about 100 mg I am not aware of any proof of deaths in either children or adults from such doses There is a statement in the literature to the effect that the smallest recorded dose which proved fatal was 95 mg in a child and 130 mg in an adult On this basis, the patient took about twenty times the fatal dose of atropine I believe that the dose of atropine stated in the literature to be fatal is much too small From experience in animals, atropine produces pronounced symptoms after very small doses due to blocking of the autonomic nervous system, but these actions are not the ones which cause the fatality, and the fatal effects require massive doses In the cat, for example, a small fraction of a mg per Kg blocks the cardiac vagus, but the fatal dose is of the order of 50 mg per Kg Humans may be much more sensitive to the fatal action of atropine, but the indications from the isolated reports of atropine poisoning are that in humans also a wide gap exists between the dose which causes very disturbing symptoms and the one which causes death For example, a 10 mg dose of atropine is apt to produce delirium, but recovery is reported from a dose as high as 500 mg In the case in question, there also remains the possibility that the child might not have swallowed all the solution that disappeared from the bottle for a 1 per cent solution of atropine is fairly bitter

I cite this case merely as an illustration of a fact which I think applies to household poisonings in general, namely, the danger of treatment When one does not know what is best to do, it is probably best to do nothing In the reported cases of poisoning with atropine, maniacal delirium fre

quently occurs and has been controlled by a barbiturate. In the case to which I have just referred, however, there was no delirium and, therefore, no indication for the use of a large dose of Amytal.

Here is the record of another inquiry. A baby was having its temperature taken by rectum. The thermometer broke and the mercury remained in the rectum. What should be done? What is the chance of serious poisoning from mercury? I have two additional inquiries of a similar nature, but in these the children bit off the bulb of the thermometer and swallowed the mercury. All of these queries were answered in the same way: Let them be and do nothing about it. The average clinical thermometer contains about a gram of mercury. There was a time when as much as 100 to 500 Gm. of metallic mercury was given orally for the treatment of ileus. In rare cases, this dose caused death. There is no doubt of the fact that some absorption takes place from metallic mercury given in bulk, but the amount absorbed from a dose given in that way must be very small. There is the account of a man who attempted suicide by injecting 2 cc. or 27 Gm. of metallic mercury into his vein; he developed some diarrhea but lived about ten years. It is otherwise when the metallic mercury is finely divided. It used to be a fairly common practice to give children as much as 100 mg. of metallic mercury in the form of a dose of 0.25 Gm. of mercury with chalk in a capsule for the treatment of syphilis. These experiences suggest that the mercury released from the broken bulb of the thermometer may be ignored with impunity. This was done in the 3 cases to which I have referred and there were no reasons to regret it.

I have a memorandum on a telephone call from a pediatrician regarding the possibility of poisoning from matches. The child was playing with a box of safety matches and chewed off the tips. Precisely how many he did not know, but he was informed that it was the contents of a nearly full

small box The problem related to the possibility of phosphorus poisoning He was reassured to learn that, to get into difficulties from that adventure, the child should have had to consume the box rather than the matches

The friction match which can be struck anywhere was originally tipped with yellow phosphorus, and 15 or 20 tips might provide a fatal dose of phosphorus But in the safety match the phosphorus is on the striking surface of the box, and even this, in present day matches, no longer contains the highly toxic yellow phosphorus but the inabsorbable red phosphorus The latter is relatively nontoxic although some contamination with yellow phosphorus is a source of danger Incidentally, even the ordinary match, which may be struck anywhere, is now relatively innocuous because the *nontoxic phosphorus sesquisulfide has replaced the yellow* phosphorus

There is here an inquiry regarding a barbiturate A baby, 7 months old, got his hands on a capsule of 0 2 Gm of Sodium Amytal, and swallowed it about 30 minutes previously There are, at this time, no appreciable effects What should be done? The suggestion was made to empty the stomach or wash it This was not imperative It would only result in eliminating the protracted period of stupor or shortening the period of deep sleep Since the total dose represented only about 30 mg per Kg, *the risk of fatal barbiturate poisoning* was negligible Considerably larger doses used to be extensively employed to induce anesthesia for surgical operations This is a good example of poisoning in which, as is very often the case, the patient does well without treatment

We recently had an inquiry about moth balls in connection with a child who had eaten some Many materials may be involved in poisoning by moth balls or other *moth repellant* articles, namely, camphor, naphthalene, and paradichlorobenzene Paradichlorobenzene is the compound now most widely used in the various forms of moth repellant materials Expo-

sure to its fumes over long periods of time causes poisoning but by oral administration the compound is relatively innocuous In the dog the feeding of 1 0 Gm per kg daily (equivalent to about 60 Gm for an average adult) for a long period of time has been found to produce no toxic effects This compound appears in the home in such forms as nuggets flakes cakes and pellets The smaller nuggets weigh about 0 25 Gm and the larger ones as much as 7 Gm Should an infant or a very young child consume 3 or 4 of the larger nuggets it is unlikely that serious poisoning would occur Some moth repellant materials contain naphthalene or a mixture of naphthalene and paradichlorobenzene We recently examined a trade box of moth balls which contained only naphthalene each ball weighing approximately 2 5 Gm Naphthalene is more toxic than paradichlorobenzene It is used in doses of 0 5 Gm in the treatment of oxyuris infestation Death has been reported in a child from as little as 2 Gm but the fatal dose of naphthalene for most cases is considerably larger It is unlikely that the consumption of a naphthalene moth ball by an infant or young child would prove serious The few recorded cases of naphthalene poisoning refer to such symptoms as abdominal cramps nausea and vomiting motor instability irritation of the urinary tract with burning in the urethra and urgency, and acute hemolytic anemia It is apparently also damaging to the liver and the kidney giving rise to jaundice and albuminuria The cases of poisoning by paradichlorobenzene in individuals exposed to the fumes for long periods of time describe injury to the liver and cataract

Camphor is now rarely found in moth balls although these are sometimes referred to as camphor balls Camphor cakes are still available and used as moth repellants It is the experience that camphor taken by mouth may cause dramatic and threatening symptoms but most patients recover We shall refer to camphor again presently

A word about the general problem of moth repellant arti

cles is in order at this point A doctor recently telephoned me about a child who had taken a quantity of a moth repellant known as Expello We examined several brands of moth repellant nuggets with the label stating clearly that these represented paradichlorobenzene However, the can of Expello gave no indication of the nature of the contents The pellets in this can had a somewhat different smell from those labeled paradichlorobenzene That threw us off the track, although we were aware of the fact that the most common moth repellants are chiefly paradichlorobenzene The manufacturer of Expello is in New Hampshire and was, therefore, not readily accessible to us, but there was inscribed on the can a label stating that it was guaranteed by the Good Housekeeping Institute We, therefore, called them up for information about this material After being directed from one person to another, the fourth person gave us the information, namely, that Expello represents paradichlorobenzene There is something wrong about having such a material which is always so accessible to children in the household without the name of the chemical clearly stated on the container It is hardly to be expected that the physician will be familiar with the chemical composition of all moth repellant articles under proprietary names which give no indication of the nature of the product It would have spared the family a good deal of anguish and the physician no end of trouble if the name paradichlorobenzene had appeared somewhere on the label, for, even if this compound might not have caused any harm by reason of its low toxicity, there is the fact that, not knowing what it is, the physician would be forced to take measures in treatment which would have been unnecessary had the name of the compound been known to him Another disturbing aspect of this experience was the fact that of the 3 cans in our possession the only one which failed to disclose the contents was the one bearing the seal of the Good Housekeeping Institute I presume that housewives take the seal of the Good Housekeeping Institute seriously

and are likely to prefer articles bearing their name Under the circumstances I wonder whether the Good Housekeeping Institute ought not to recognize a moral obligation in the matter and insist on the chemical name appearing on the container of articles which may rightly or wrongly find their way into the mouth of a youngster rummaging about in the house A person in charge of these matters in the Institute informed me that the label was entirely adequate within the meaning of the law and that this moth repellant Expello did not fall in the class of so called economic poisons We should take cognizance of the fact that a substance which is not classed as a so called economic poison is not necessarily nontoxic The criteria for an economic poison merely differentiate between those articles which take small doses to kill and those which require somewhat larger doses to kill For example in an extreme case if the average lethal dose per Kg were 49 mg it would be classed as an economic poison whereas if the average lethal dose were 51 mg the article would stand outside of the class of economic poisons I think this is not an improper place to suggest that something be done to ensure that when a doctor is called upon to treat a possible case of poisoning by a common household material the label on the container inform him of the exact nature of the chemical and the amount of it that is present in the preparation Without such information he is often quite helpless

Camphorated oil is sometimes mistaken for castor oil and it might be well therefore to know something about the toxicity of camphorated oil Camphor is a convulsant but it is very rapidly eliminated so that even after a fairly violent convulsion the individual is likely to recover While there are a great many cases of camphorated oil poisonings the number of deaths is very low even in cases in which violent convulsions have occurred Camphorated oil is a 20 per cent solution of camphor in oil and the smallest oral doses of camphor which are on record as causing death are of the order of 1 5 Gm That

would make about 2 teaspoonfuls of camphorated oil There have been instances of mass poisoning by camphorated oil In one series, each of some 20 children received from 1 to 1 5 tablespoonfuls of camphorated oil Most of them developed convulsions, but they all recovered

Infants and children seem to have little trouble in getting hold of a bottle or can of kerosene or gasoline Also, they do not seem to have any particular aversion to drinking it There are still places in the country in which kerosene is used in doses of a few cc for the treatment of bronchitis and colds ' A considerable number of cases of poisoning are encountered There are recoveries from as much as 125 cc of kerosene and deaths from as little as 30 cc There is a case of an adult who recovered from 750 cc There is not enough information to be certain whether kerosene or non leaded gasoline is more toxic The course of kerosene poisoning is very rapid Effects appear within a few minutes with gastrointestinal symptoms (vomit ing, diarrhea, abdominal cramps) and central nervous system symptoms (coma, convulsions) About 5 to 10 per cent of cases die, and this takes place in less than 24 hours The remainder seem to recover completely and fairly promptly It is fairly safe to assume that the patient who is still alive on the day after a dose is likely to recover It behaves in many respects like a volatile anesthetic The lungs seem to be involved in a large proportion of the cases and such a case may be mistaken for one of primary pneumonia It is not certain how the lungs be come involved, whether by excretion of the volatile agent through the lungs or aspiration during vomiting It is note worthy that, in animal experiments, the fatal dose by stomach is about ten times that by intratracheal injection This may indicate rapid absorption from the pulmonary bed or marked inflammatory reaction to the high concentration It is obvious that the stomach should be washed if the time interval suggests that any appreciable amount may still be there, and special care needs to be taken to avoid aspiration The pneumonitis

that develops may be treated by the usual measures oxygen and antibiotics There are no specific antidotes

Boric acid and borax (sodium borate) are common house hold chemicals intended either for use as eyewash or anti septic solution or to sprinkle around the borders near the door to discourage ants There are many other uses They are often put up in packages which are almost indistinguish able from the package of bicarbonate of soda I have often wondered why we don t see more cases of boric acid poisoning It seems to be so easy for a person who gets up in the middle of the night to take a dose of bicarbonate of soda to take in its place a teaspoonful of borax It has no distinctive taste or smell In spite of this cases of boric acid poisoning in the household are not numerous

I had one inquiry about a person who swallowed about 4 ounces of a solution containing approximately 6 Gm of boric acid He vomited promptly Such a dose in adults is not apt to cause serious injury and since he seemed to have emptied his stomach fairly well within a few minutes the doctor was ad vised to do nothing about it There was a follow up in this case and it was established that it had caused no poisoning I have here the record of another inquiry from a pediatrician The mother made up the 24 hour formula for her twins and she put 60 Gm of boric acid into the solution in place of one of the sugars The error was discovered at the end of the day when all of it had already been given It was estimated that about one half of each feeding had been vomited so that each baby presumably retained 30 Gm of boric acid The babies were well 48 hours later without any treatment That is much too long a time without symptoms after a toxic dose of boric acid The toxicity of boric acid does not seem to be as great as is indicated by the statement found in the literature that 5 Gm may be fatal to a baby and 15 Gm to an adult There must be very marked individual differences in susceptibility There is here in my folder another story about boric acid

The mother baked a cake and put in a teaspoonful of boric acid instead of baking soda The baby ate a piece of the cake Later in the day the mother discovered the error and tele phoned to her pediatrician He found nothing wrong with the baby He was advised to do nothing about it Nothing hap pened to this child But the mother had another question namely, ' Is the cake spoiled? ' Apparently it was not as satis factory a cake as it might have been if it had been made with bicarbonate of soda I suggested that the cake was edible but that it would not be wise to permit one member of the family to eat it all The 5 Gm of boric acid could do no harm when distributed among the members of the family

I am, of course, speaking only of household accidents, and not of errors of medication You are undoubtedly aware of the disasters which have occurred in hospitals, where boric acid was used in place of sodium chloride for intravenous infu sions The occurrence of such accidents has created quite a furor in recent years The question has been debated whether boric acid should not be colored to distinguish it more readily from harmless materials The whole question of the utility of boric acid has been reviewed There seems to be considerable doubt concerning its value as a medicinal agent, and some hospitals have deleted it from their formularies

Poisoning by boric acid causes fairly prompt gastrointestinal symptoms, such as vomiting, abdominal cramps and diarrhea symptoms of circulatory collapse, coma or convulsions skin eruptions nephrosis and anuria There is no specific antidote

Dr John B Deitrick Would you say how you would treat poisoning by atropine?

Dr Gold I know of no specific antidotes to the fatal action of atropine The only treatment is supportive, and the meas ures that one might use will depend on the symptoms which seem to be most threatening in the particular case If the patient presents respiratory depression with cyanosis, one might use oxygen If there is troublesome delirium or con

vulsion one might quiet the patient by appropriate doses of the barbiturates Hyperthermia which may result from suppression of sweating can be managed by sponging There are specific antagonists to atropine such as Prostigmine and Mecholyl but it is doubtful whether any safe doses of these can prevent the fatal action of atropine

Student How about the use of pilocarpine?

Dr Gold The same applies to pilocarpine It is extremely doubtful whether any amount of pilocarpine would counteract the fatal action of atropine

Dr McKeen Cattell The reverse would be all right, would it not?

Dr Gold Yes atropine is a highly effective antidote against poisoning by the parasympathetic drugs By means of atropine an animal can be saved from as much as 10 times the fatal dose of physostigmine

Dr Helpern you see a great many cases of poisoning in the Medical Examiner s Office Would you tell us something about these?

Dr Milton Helpern Those in the Medical Examiner s Office are of course fatal cases of poisoning We encounter a large number of them in a year Unfortunately our department has no record of the nonfatal cases There is no agency in the city through which the nonfatal cases are cleared One would have to comb the hospitals and the records of private physicians in order to secure the information on the total incidence of poisoning A large proportion of the poisonings which we encounter are caused by ordinary household materials

Illuminating gas is the chief cause of poisoning that we see The toxic agent in it is carbon monoxide and the latter is responsible for more than half of all our cases

The extermination of household pests provides a rich and varied source of household poisons I might refer to a few of the more common ones which come to our attention They are

supplied under a wide variety of trade names There is the roach paste known as the John Opitz roach paste, which is widely advertised It reeks of yellow phosphorus It is usually placed on pieces of potato or bread under the kitchen sink Not infrequently the creeping child gets hold of one and munches on it Since these preparations usually contain from 3 to 5 per cent yellow phosphorus, the child need only consume a gram or less to be seriously poisoned It sometimes develops acute gastrointestinal symptoms which direct attention to the poisoning, but the effects may come on more insidiously with signs of acute hepatitis, and often the poisoning is not suspected until irreversible symptoms have developed Poisoning by yellow phosphorus in little children munching on fire crackers on the Fourth of July is no longer a serious problem in communities where the use of fireworks has been controlled There is the more commonly used roach powder which may represent almost pure sodium fluoride Some protection against poisoning by this material is afforded by the recent law which requires the use of some distinctive dye, such as indigo, to color it blue You may recall the report, some time ago, of the group of fatalities in an institution in Oregon where the cook confused the fluoride with flour I might state that most of the fluoride poisonings which we encounter here are the result of attempts at suicide

The rat poison is another exterminant which plays an important part in household poisonings The most common agent is white arsenic The preparation we have encountered comes in a little round wooden box, labeled Poison ' Perhaps the label is responsible for so many cases of suicide with arsenic I recall one instance of homicidal arsenic poisoning in which a demented sister treated one brother with it on one day, and the other the next day The clinical picture, marked chiefly by gastrointestinal symptoms and collapse, is easily confused with other conditions and, in the instance I just mentioned, the diagnosis of botulism was made It is unfortu

nate that physicians do not more often include poisoning among the possibilities when the diagnosis of an unusual disease is considered. I do not know of a case of suicide with arsenic in which the diagnosis was made during life. In the case of the two brothers which I just mentioned it is possible that a prompt and accurate diagnosis in the first might have prevented the second poisoning.

An insecticide which sometimes causes poisoning is one containing nicotine. These preparations contain about 40 per cent nicotine sulfate and are used as plant sprays. It causes nausea, vomiting, prostration, and sometimes convulsions. It is rapidly fatal in doses of the order of about 50 mg.

Cleansing agents are another fruitful source of household poisonings. There are the strong alkalis, such as lye, concentrated ammonia, and washing soda. Every so often baking soda is confused with washing soda, and the concentrated sodium carbonate causes serious corrosion. Similar lesions are produced by lye and concentrated ammonia. Strong acids are sometimes found in the home, hydrochloric acid, sulfuric acid, and nitric acid. We had the case of a child who drank the soldering fluid the father used in tinkering with electrical equipment. It is a concentrated mixture of zinc chloride and hydrochloric acid, and produced intense corrosion.

Dry-cleaning fluids and stain removers are very common household poisons. The more common ones represent carbon tetrachloride or mixtures with carbon tetrachloride, solvent naphtha, turpentine, benzine, gasoline, and kerosene. Cases of poisoning result both from the inhalation of vapors as well as from ingestion. Some time ago we examined the body of a woman who had cleaned a dress with carbon tetrachloride in the bathroom, a small space without ventilation; she succumbed to the fumes of this compound.

Some potent metal cleansers contain cyanide. These solutions find their way into the home without proper labels. The cyanides are commonly used in silver polish. Cyanide is very

effective in taking tarnish off silver It also lends itself to use for suicide There used to be a preparation known as "Quick as a Wink" and another, "Cinderella" shoe polish, for cleaning metal finished shoes One of these preparations suggested an antidote on the label, "If taken by mistake, throw cold water on the face,' and I suppose that was about as useful as any other

The disinfectants commonly found in the home include such articles as tincture of iodine, carbolic acid, compound cresol solution (Lysol), and creosote mixtures Most of these produce not only systemic poisoning but local corrosive action as well

I should not omit alcohol, the effects of which are well known In this connection the solid wood alcohol mixtures, such as Sterno and Dry Heat, present a much more serious problem Alcoholics sometimes resort to these in extremity to prolong an intoxicated state Rubbing alcohol and other medicated alcohols are also used for this purpose

Black shoe dye often contains nitrobenzene It is a potent poison As little as 1 cc may prove fatal, although 30 cc have been survived It is readily absorbed through the skin of an infant's foot as well as by inhalation It causes bizarre symptoms involving the gastrointestinal tract, the central nervous system, and the viscera Marked methemoglobinemia is an outstanding effect

Dr Gold Dr Dale is here from the Department of Pediatrics It would be interesting to learn about the experience of the pediatrician in this hospital

Dr John H Dale, Jr Our experience is in general agreement with your statement, Dr Gold A considerable proportion of the children admitted to this hospital present the problem of poisoning with household drugs, medications, and other materials Most of our cases are between 2 and 3 years old The most frequent poison is the fluoride roach powder As a rule, we see the children very soon after they have taken

it Gastric lavage is usually performed in the clinic The signs and symptoms which follow are those of gastroenteritis and so far this has responded satisfactorily to bland diet and fluids We recently saw a child who bit off the tip of a thermometer and swallowed the mercury It passed through the intestinal tract in about 3 days It developed no signs of poisoning The laxative known as Ex Lax which contains phenolphthalein is another source of trouble for us The usual story when they are brought in is that they have consumed from 12 to 24 of these chocolates Except for purgation nothing seems to have happened One child that took hydrochloric acid developed burns in the buccal mucosa and a gastroenteritis There was no bloody diarrhea The recovery was uneventful Children are commonly brought in with the story of having eaten a box or a book of safety matches In view of the fact that the phos phorus is on the striking surface we have considered it safe to send these children home without treatment We have seen a few cases of lead poisoning usually in children with hysteria or pica who have taken to eating the paint on the stairs win dow sills and elsewhere These have been of the chronic not of the acute type of lead poisoning This about sums up the chief types of cases which we encounter in this neighborhood There have been no lye burns and no caustic poisonings of any kind

Dr Gold Did most of the children whom you have seen re cover?

Dr Dale All of them recovered We have had no deaths *from household poisonings in the past 3 years*

Dr Gold Even all the cases who took fluoride in the form of roach poison?

Dr Dale Yes Of course we do not know how much was taken in these cases The story is usually obtained from an extremely excited mother and it is difficult to learn how much was taken but it seems that the children rarely take too much Our experience bears out your point that overzealous treat

ment causes more trouble than the poison As I stated, we lavage the stomach with tap water and call it quits We keep the child under observation for changes in the pulse and for symptoms referable to the central nervous system We treat the gastroenteritis with a bland diet That seems to have been enough for our cases

I might refer to the few cases which we have seen in which the child swallowed furniture polish In these we have not been able to identify the toxic ingredients Fortunately all of these recovered We have seen 2 cases of acute alcoholism in children less than 10 years of age One of these could hardly be considered an accident, since the family fed the child almost a pint of wine The other was an 18 month old infant who got his hands on a pitcher of beer and drank quite a bit of it Both recovered

When we go back further in the history of this department we find some cases of poisoning by boric acid, hyoscine, atropine, and codeine Most of these were therapeutic poisonings We have not had any of these in recent years

Dr Cattell Might you have used calcium in the fluoride cases?

Dr Dale We did not use it

Dr Gold Are you referring to the value of calcium as a systemic antidote or for its effect in the gastrointestinal tract?

Dr Cattell I had in mind the fluoride in the stomach The sodium fluoride would be converted into the extremely insoluble calcium fluoride if the stomach were washed with the soluble calcium chloride

Dr Helpern In your cases Dr Dale, was the fluoride recovered and identified by chemical analysis?

Dr Dale No We knew the brands of roach powder, and the composition was supplied by the manufacturer

Dr Helpern I ask this because fluoride is a very potent poison and it does not take very much of it to kill

Dr Gold One has to take from 5 to 10 Gm to produce seri

ous poisoning in an adult. Most of the roach powders, I think, contain somewhere from 30 to 90 per cent sodium fluoride. In the case of the 30 per cent preparations, one would need to consume from 15 to 30 Gm. of the powder. That would be quite a meal.

Dr. Helpern: From what I have seen, Dr. Gold, one does not have to eat very much of it to get into trouble. I would recommend only very small doses of the roach powder.

Dr. Gold: Dr. Dale, I surmise from what you have said about the management of the cases in which a household poison has been taken, that it is wise merely to wash out the stomach, observe the patient for a suitable time, and then treat special symptoms as they arise, and that you refrain from the use of stimulants and depressants unless there is clear indication for them.

Dr. Dale: That is the policy we have followed. The head of our department, Dr. Samuel Z. Levine, believes that that is the wisest course.

Dr. Cattell: We have not said much about therapy in this conference. Perhaps we should have another session for that.

Dr. Gold: Much remains to be said about therapy of household poisonings, and I think that it is a good suggestion to pursue the matter of treatment in another conference.

SUMMARY

Dr. Gold: The nature of the problems of household poisonings was explored in the conference this afternoon. The number of chemicals which may be involved in household accidents is extremely large. No attempt, therefore, was made to exhaust the subject. The comments were confined to some of the more general aspects of the situations and to examples of some of the more common and interesting experiences. While there is fairly abundant information concerning poisons in the numerous texts on general toxicology, industrial toxicology, pharmacology, and special articles in the medical literature,

these often fail to provide the answers to the specific problems which the physician encounters in the case of a household accident For example, information on the toxicology of mercury is abundant and readily accessible, but the case of the child who has bitten off the tip of the thermometer and swallowed it, presents a special situation, the same is true for the toxicology of nicotine, but it doesn't quite cover the case of the child who has been munching on cigarettes In these cases, it would help to have at hand such facts as the chance of poisoning or the amount of cigarette tobacco babies are in the habit of eating

Most accidental household poisoning occurs in infants and young children who go exploring about in the home swallowing chemicals without discretion There are such items as laxative pills containing strychnine, chocolate cathartics containing phenolphthalein, eye drops containing atropine hypnotic capsules containing a barbiturate, matches moth balls containing camphor, naphthalene, or paradichlorobenzene kerosene or gasoline, roach poisons containing phosphorus or fluoride, rat poisons containing arsenic, furniture polish and shoe dyes These and a few others such as borax taken accidentally in place of a dose of bicarbonate of soda, or put into a cake by mistake in the place of baking powder, or into the infant s formula in the place of a sugar, received attention in the discussion

Sodium fluoride is a violent poison, but the pediatricians pointed out that, while one of the common experiences at the New York Hospital is the case of the excited mother with the child who had been trying out roach powder containing sodium fluoride, they have encountered no cases of serious poisoning with this material in recent years, although most of them received little or no treatment There seems to be a wide gap between the accidental taking of a household poison and serious poisoning by it Apparently the amount taken is usu

ally too small This is a matter of some importance for so often the real trouble is caused by overzealous treatment

Unfortunately many of the preparations containing poisons to which children are exposed in the home fail to provide the physician with a clue to the essential chemical There was strong feeling in favor of extension of legal requirements for the appearance of the name of the compound on the label to guide the physician to appropriate measures, to allay panic, and to prevent unnecessary treatment

At the end of the session today, the problems relating to several other agents which participate in household poisonings remained in need of attention also some of the more specific methods of treatment These will be considered in a subsequent conference

Dr. Gold: I should like to say a few words about the cigarette as an item in household poisoning. Babies sometimes eat cigarettes. I have in my file an account of such a case. The mother discovered that her one-year-old baby had eaten 2 cigarettes. She administered milk and the baby promptly vomited the milk together with about one-fourth of the tobacco. What remained represented about 45 mg. nicotine, or approximately 4 times the lethal dose for a 10-Kg. infant. When the doctor arrived about 3 hours later, the baby seemed weak and listless. He administered some syrup of ipecac but this failed to produce vomiting. He was advised to wash the stomach with a 1:10,000 solution of potassium permanganate, and to leave a few ounces of the solution in the stomach. This was promptly carried out, and no further signs of nicotine poisoning developed. It is difficult to be certain whether these measures played any part in the uneventful recovery. The potassium permanganate was a rational procedure because nicotine is very rapidly destroyed by this oxidizing agent. Little is known of the hazard of nicotine poisoning when cigarettes are eaten. The alkaloid, nicotine, is a violent poison and is absorbed from mucous membranes within a few minutes. A cigarette contains about 30 mg. of nicotine, and the fatal dose of nicotine for a man is of the order of 60 mg., the content of about 2 cigarettes. It seems, however, that nicotine is not nearly as serious a danger when taken by mouth in the form of cigarettes. We administered enormous doses of cigarette tobacco by stomach tube to cats, doses as high as 2 Gm. per Kg., which represented as much as approximately 60 mg. of nicotine per Kg., or about 6 times the lethal dose for cats. Symptoms appeared very quickly; within a few minutes, the animal showed twitching of the ears, then nausea, and within 15 minutes or less there was vomiting with expulsion of the tobacco. That was all there was to it; within a few hours all 10 animals were well. In 2 additional animals, morphine was given to prevent vomiting, and these died of nicotine poison-

ing Apparently, the absorption of nicotine from tobacco taken by mouth is markedly delayed, and there is indication from experiments in animals that nicotine is less than one fifth as toxic when taken in the form of tobacco The fairly prompt vomiting induced by the absorption of the initial fraction is, of course, a factor of safety

In recent years, a few highly effective and specific antidotes to some poisons have been developed Dr Riker, would you say a few words about the specific treatment of poisoning by arsenic?

Dr Walter F Riker BAL, or 2,3 dimercaptopropanol, is a specific antidote to poisoning by arsenic The details of its actions were discussed in the therapy conference on BAL which was published in Volume III of the *Cornell Conferences on Therapy* A few significant points might be mentioned here This material is now Council accepted, and is available in the form of a 10 per cent solution in peanut oil in ampoules containing 4 5 cc. The sulfhydril groups in BAL compete with the sulfhydril groups of tissue enzyme systems for the arsenic, and in that way the tissues are protected against arsenic BAL has such a strong affinity for arsenic that it may even remove the metal from combination with protoplasm This is an important aspect of its use as an antidote if tissue damage has not progressed too far BAL exerts its protective action by increasing the excretion of arsenic in the urine and also by the fact of the conversion of arsenic into a dithioarsenite which is relatively nontoxic Most of the experimental and clinical experience relates to the treatment of poisoning by therapeutic arsenicals, such as Mapharsen In such cases, doses of the order of 5 mg per Kg, or about 300 mg (3 cc of the 10 per cent solution) may be given intramuscularly every 3 or 4 hours as long as seems to be indicated by the evidence of arsenic poisoning BAL has toxicity in its own right, causing lacrimation blepharospasm, vomiting, unrest, paresthesias, and muscular cramps When these symp

colored blue has something to do with it There is also the fact that many less dangerous materials for antiseptic washes have become more popular The condition, however, is far from rare Longcope and his associates assembled 42 cases in a period of about a year in Baltimore in connection with their study on BAL which was published in the July, 1946, issue of the *Journal of Clinical Investigation* Past experience left one in some doubt as to the possibility of any antidote or method of treatment proving successful in poisoning by mercuric chloride because of the extraordinary speed with which this compound produced irreversible damage in the gastrointestinal tract, locally, and in the kidneys, systemically Dr Gold, you recall the case we had here in the hospital several years ago, at the time we were studying sodium formaldehyde sulfoxalate, which had been proposed as an antidote This compound offered considerable promise because it was relatively innocuous and could be given in large amounts by mouth and by vein It promptly precipitated the mercury which was in the gastrointestinal tract and in the blood stream, and the precipitate was much less toxic. This was an 18 year old girl who swallowed 1 Gm of bichloride of mercury in a half glass of water She vomited almost immediately Active treatment was started in the hospital about 30 minutes after the drug was swallowed She received abundant washing of the stomach, colonic irrigations, intravenous infusions of sodium formaldehyde sulfoxalate, and gastrointestinal washings and irrigations with the same compound The whole situation seemed to have been most favorable for protection by the new antidote, in fact most favorable for recovery even without an antidote In spite of it all, poisoning progressed and in 2 weeks she died in uremia The use of BAL has created a most dramatic change in the outlook for patients in poisoning by mercuric chloride The experience of Longcope and his associates shows that recovery is now assured after even 1 Gm or more taken several hours previously with the proper use of

BAL as an antidote. Some of their cases were in a desperate state of poisoning at the time that therapy was started. With rare exceptions, recovery was complete in a matter of several days to 3 weeks. In one case, the dose of poison was enormous, 20 Gm.; in another case, the delay in starting the treatment was very long, 19 hours. There is evidence that mercury poisons the tissues by a mechanism similar to that of arsenic. There is also fairly strong evidence that the BAL can withdraw mercury from its combination with tissue proteins and in that way reverse damage. There has been no experience, as far as I know, with the use of BAL for stomach lavage in the case of bichloride of mercury poisoning There can be no doubt of the wisdom of emptying and washing the stomach at the earliest possible moment, even though such a potent systemic antidote is available. The most favorable schedule for the use of BAL in poisoning by bichloride of mercury is similar to that already described in the case of arsenic poison[illegible], 5 mg. per Kg. [illegible]
as sc[illegible]
tom[illegible] [illegible] an individual unduly sensitive to it.

In regard to lead poisoning, Dr. Gold, you asked whether children still are poisoned by eating the paint off their cribs and toys. That source of danger has been greatly reduced because these items are now quite generally covered with paint which does not contain lead, although when the father repaints them he may use paint containing lead pigments. In infants and children, eating the paint [illegible]
work[illegible]
In [illegible]
po[illegible]
Dep[illegible] Hospital. Most cases of lead poisoning are of the chronic variety, whether in children or in adults. The recognition of lead poisoning is not easy. The symptoms develop insidiously and resemble many other

sues There are several measures which promote this process, namely, low calcium, high phosphorus, systemic acidification, and parathyroid hormone. In such cases the patient may receive a diet which contains little or no milk and no vegetables or fruit The diet consists mainly of meats, fats, and cereals Ammonium chloride in doses of about 5 to 8 Gm daily helps to shift the acid base equilibrium toward the acid side The parathyroid hormone may be given in doses of 100 units once or twice a day intramuscularly to promote the mobilization of lead from bone (which follows the course of calcium), and to promote its excretion in the urine Various methods for "de leading" differ in details, but they are essentially similar in principle to the measures I have described "Deleading is best carried out in a hospital

On the whole, the results of treatment in lead encephalitis are not very satisfactory Hypertonic solutions of glucose may help temporarily to control symptoms due to high intracranial pressure Spinal tap to lower pressure may be of some value Permanent injury of the brain as the result of the high intracranial pressure is common in survivors of lead encephalitis

Dr Gold Accidental cyanide poisoning in the home is a very rare occurrence in these days, but there are about 25 hydrocyanic acid and cyanide deaths a year in New York City involving industry, fumigation, homicides, suicides, and other means of exposure to this violent poison Seeds of various fruits, such as apple, peach, plum, cherry, may cause poisoning, and there was a report of human poisoning from the eating of chokecherry seeds a few years ago I recall an experience with one of the persons in the department of chemistry several years ago She was drawing up cyanide solution in a pipette and some of it came up into her mouth She promptly spat and rinsed her mouth thoroughly She thought the danger under the circumstances was negligible, but she couldn't dismiss it altogether About 30 minutes later she began to feel faint and giddy, and ran upstairs to our laboratory for advice She was

pale and her pulse was rapid There was no satisfactory treatment at that time, and since about 45 minutes had elapsed without progression of symptoms, she was assured that the danger was negligible Her symptoms improved quite promptly I am inclined to think it was a case of panic Had this occurred today, I might have turned to more certain antidotes Dr Cattell, would you say a few words about the present treatment of cyanide poisoning?

Dr McKeen Cattell It has long been known that methylene blue, the nitrites, and sodium thiosulfate or 'hypo' are effective in cyanide poisoning The more recent experiments of Chen and his collaborators have resulted in a plan of treatment in which both nitrites and thiosulfate are used in such a manner that dogs recover from as much as about 20 times the fatal dose of cyanide Either drug alone protected against only about 5 fatal doses of cyanide They suggested the intravenous injection of 0 3 Gm sodium nitrite (10 cc. of a 3 per cent solution) in a period of 2 to 4 minutes This is to be followed promptly by an intravenous dose of 12 5 Gm of sodium thiosulfate (50 cc of a 25 per cent solution) injected over a period of about 5 to 10 minutes It is recommended that one half the dose of the two drugs be repeated in about 2 hours, and that the patients be kept under observation for 24 hours or longer for the possible need of further treatment

Visitor Is there time enough to get such treatment going in the case of cyanide poisoning as it occurs in humans?

Dr Gold One has to anticipate such poisonings and make some preparation for them Chen and his collaborators suggested a small kit containing 2 ampoules of 10 cc each of 3 per cent sodium nitrite 2 ampoules of 50 cc each of 25 per cent sodium thiosulfate, and a sterile 10 and 50 cc syringe with needles It is also to contain 12 pearls of amyl nitrite The patient may be given amyl nitrite by inhalation as an antidote to tide over the period required for the

preparation of the solutions. Neo-synephrine or Pared may be given in 5 or 10 mg. doses by intramuscular oı travenous injection to counteract the vasodepression caı by the nitrite.

There is no doubt of the need for speed in cases of man cyanide poisoning. Symptoms occur in rapid successi giddiness, faintness, vomiting, respiratory stimulation lowed by depression, coma, and convulsions. Only 30 min may elapse before the respiration stops, but in some cas period of 2 to 3 hours may be available for the applicaı of the antidotes. There are chances for recovery as lon; the heart beats, and additional time is gained by artifi respiration in the event that breathing has ceased. There now records of many cases of cyanide poisoning in hum in which these antidotes have proved effective. The eff are dramatic; poisoning in which there was coma and] found respiratory depression has been reversed in a few n utes after the injection of the antidotes.

Student: Cyanosis is often mentioned as a symptom cyanide poisoning. I was wondering about that since cyan is supposed to poison the respiratory catalysts so that tiss cannot take oxygen out of hemoglobin and venous blood mains brighter red than normally.

Dr. Gold: That is correct, and at the onset of poison the patient is not cyanotic. He only becomes so late in p soning when there is profound respiratory and circulat failure.

Student: No mention has been made of vomiting or g tric lavage in the treatment of cyanide poisoning. Is it sorbed so fast that this measure is of no importance?

Dr. Gold: Prompt emptying of the stomach is importa also lavage with an oxidizing agent like solution of hydrog peroxide diluted 10 times, or 1:10,000 solution of pot sium permanganate. If the patient is in coma, it may be i possible to produce vomiting; also, vomiting and washi

the stomach in such patients carry the danger of aspiration pneumonia.

Dr. Janet Travell: Perhaps it is unnecessary to state that apomorphine should not be used in comatose patients. Yet I saw a patient who had taken Lysol and had become comatose, to whom apomorphine was given to induce vomiting. Emesis did not take place, and within 3 or 4 minutes there ensued a very profound respiratory depression which necessitated the use of carbon dioxide and oxygen. Apomorphine often fails to cause emesis in comatose patients.

Dr. Cattell: It is a known fact that, during coma, apomorphine markedly depresses the respiratory center.

Student: How do the antidotes to cyanide work?

Dr. Gold: Dr. Bodansky, you experimented on the problem of cyanide poisoning during the war. Will you tell us something about the mechanism of action of the antidotes and also about your experiences?

Dr. Oscar Bodansky: The treatment recommended by Dr. Chen rests chiefly on experiments in which the effect of amyl nitrite inhalation or of the intravenous injection of sodium nitrite, accompanied in either case by the intravenous injection of sodium thiosulfate, was determined in animals receiving sodium cyanide by subcutaneous injection. In such cases, there is an opportunity for methemoglobin to form from the action of the nitrite, while the cyanide is being absorbed into the circulation. The conditions here are similar to those in poisoning by oral ingestion of cyanide. The methemoglobin and thiosulfate greet, as it were, the entering cyanide and detoxify it. The methemoglobin does so by forming cyanmethemoglobin, and the thiosulfate by forming thiocyanate.

We were faced with a somewhat different problem in our investigations during the war. In poisoning by inhalation, the hydrocyanic acid or cyanogen chloride enters the circulation very rapidly, and a lethal amount may paralyze tissue

respiration before therapy can be instituted We wanted to know whether an already established lethal degree of cyanide poisoning could be reversed by the rapid induction of methemoglobinemia In poisoning under the circumstances we were considering the inhalation of a lethal dose might occur very rapidly, indeed within a few seconds and death might follow within a few minutes, so that the application of intravenous therapy might be impractical We therefore, tried to determine how effective the prompt induction of methemoglobinemia by the inhalation of amyl nitrite would be under these conditions, and, further, to what extent the prophylactic induction of methemoglobinemia would be effective in counteracting the result of anticipated exposure to a lethal dose of hydrocyanic acid or cyanogen chloride

We exposed a number of dogs in pairs to an approximately lethal dose of hydrocyanic acid in a gas chamber One dog in each pair was given artificial respiration and treated with amyl nitrite about a half minute after removal from the chamber, while its partner served as a control, receiving only artificial respiration It was found that amyl nitrite exerted a significant therapeutic effect when cyanogen chloride was the toxic agent, but not in the case of hydrocyanic acid On the whole, treatment after exposure to a lethal dose by inhalation proved unsatisfactory, and so we turned to the problem of prophylaxis We induced methemoglobinemia in a number of dogs by oral or intramuscular administration of PAPP (p-aminopropiophenone) The results were very striking The dose of hydrocyanic acid tolerated by methemoglobinemic dogs proved to be, in general, proportional to the degree of methemoglobinemia The latter protected against 2 to 8 times the dose of cyanide which would be lethal to over 90 per cent of unprotected animals One dog in which a 49 per cent methemoglobinemia had been induced withstood an exposure about 40 times the dose lethal

to unprotected animals We obtained similar prophylactic effects against poisoning by cyanogen chloride

In the course of exposing a considerable number of animals we found that, with one or two rare exceptions the animals either died promptly, that is within periods ranging from a few minutes to hours, depending on the dose, or else they recovered completely, after periods of incoordination and a semistuporous state lasting not more than a few hours I recall one animal which recovered from the acute effects but became blind, could not feed itself, and would not swallow This corresponds I believe, quite well with the experience in man In fatal cases the course is usually acute in the others recovery is complete There have been one or two reports of neurologic or psychologic derangements lasting for from one to several weeks after the acute effects of cyanide poisoning but recovery ultimately appeared to be complete

Dr Gold In the brief period that remains, it might be well to discuss a few of the general problems that arise in cases in which a household poison has been swallowed Are there any questions?

Dr Cattell In a case in which bichloride of mercury has been taken, I wonder whether it would not be well to give a large dose of albumen or starch solution before the stomach tube is used, and follow this by an attempt to secure vomiting with the finger?

Dr Gold What do you think about that, Dr Modell?

Dr Modell I would agree with that I would give something by mouth if it were available, and then attempt to induce vomiting

Dr Gold Milk is likely to be at hand in the household What would you think about using that first?

Dr Modell Yes milk or eggs Also, I have found it easy to induce vomiting by putting the finger way down into the throat

from the stomach. They are not absorbed from an acid m dium, whereas many other substances are.

Dr. Cattell: Just the fact that a poison is dispersed in large volume of liquid may account for delay in absorptio This is well illustrated by alcohol which is absorbed to a co siderable extent from the stomach. The case of alcohol al illustrates the role of milk. It is well known that alcohol take with milk produces much less marked effects.

Dr. Gold: Potassium permanganate is used a great deal fo gastric lavage in the treatment of poisonings. Dr. Travell, wi you tell us how one would go about using it.

Dr. Travell: Potassium permanganate is used for oxidatio and destruction of alkaloids and other organic poisons. It i not equally effective against all of them. For example, i rapidly destroys strychnine, nicotine, physostigmine, an quinine, but is ineffective against caffeine, atropine, pilc carpine, and cocaine. The most desirable concentration fo gastric lavage is about 1:10,000. A 1:10,000 solution is clear transparent, and violet in color. The solutions which ar recommended in some handbooks of toxicology are often de scribed as pink. These may represent concentrations of abou one part in a million and may not contain enough potassium permanganate to do any good. To make up a solution of a suitable concentration quickly, take about half a teaspoon ful of the crystals, which weighs about 5 Gm., and dissolve it in a pint of water. This produces approximately a 1 per cent solution. Two teaspoonfuls of the latter dissolved in a quart of water produce a satisfactory lavage solution, about 1:10,000.

Dr. Cattell: That is much more dilute than the concentration usually recommended.

Dr. Travell: The dilutions which are recommended vary from a 1:250 solution to one which is described as pink. The stronger concentrations are so irritant that they usually induce vomiting by local action.

Dr Gold Potassium permanganate itself is toxic Doses of the order of 2 or 3 Gm have caused death in humans This fact is sometimes overlooked One well known textbook on forensic medicine recommends putting as much as 25 Gm of potassium permanganate into the stomach

Dr Cattell Are we to understand that we should not use solutions stronger than 1 10 000?

Dr Gold If you use solutions much stronger than 1 10 000, you would induce vomiting which might not be a bad thing in a patient who swallowed a poison But the fact is that potassium permanganate, 1 5,000, is irritating to the gastric mucous membrane, and it is wise not to use one stronger than that The 1 10 000 solution should take care of all the needs with less risk of damage

SUMMARY

Dr Gold The conference today winds up our discussion of household poisoning the first having been held a week ago In the two periods, a fairly large number of materials came under consideration laxative pills containing strychnine, chocolate cathartics containing phenolphthalein, eye drops containing atropine, tablets or capsules containing barbiturates matches, cigarettes mercury of the clinical thermometer, lead in the paint of the furniture, borax, moth balls and other moth repellants, roach poisons of phosphorus or fluoride, rat poisons of arsenic, furniture polish shoe polish, kerosene gasoline, and a few others This is only a small sample of all the chemicals which present problems in household poisoning but it apparently provided us with sufficient examples of the nature of the problems to stimulate fruitful discussion It is not uncommon that adults are poisoned accidentally by materials in the medicine chest There is the case of the person getting up at night to take a dose of bicarbonate of soda and finding that he has swallowed a teaspoonful of borax which not infrequently comes in similar

such symptoms have any bearing on the lethal action of the poison, for if they have not, the patient is likely to be better off with an opportunity for the effects of the drug to wear off by elimination

It is useful to bear in mind the point that poisons taken in the forms in which they are encountered in the household sometimes present quite a different problem from that which one might infer from the descriptions in texts on toxicology The case of nicotine is a good example A child may swal low the tobacco of 2 cigarettes which contain more than a lethal dose of nicotine but it is likely to get into very little trouble because the first portion absorbed causes sufficient vomiting to expel the remainder of the tobacco, and there are the experiments in animals showing that nicotine in the form of tobacco taken by mouth is only about one fifth as toxic as the poison taken as such

There was no tendency in these conferences to minimize the hazards of disaster from household poisons, but the at tention called to the relative infrequency of disasters because of the conditions under which infants and children go about the matter of sampling poisons is worth bearing in mind in order to avoid undue panic on the part of the family and overzealous treatment which may do more harm than good

For the vast majority of poisons there are no specific anti dotes If there is reasonable suspicion that a serious quantity of poison has been consumed delaying absorption, washing the stomach, and the treatment of hazardous symptoms are obviously necessary There was some discussion of the utility of various measures The extraordinary efficacy of BAL as a specific antidote in the treatment of bichloride of mercury poisoning and arsenic poisoning, the various measures which prove useful in lead poisoning and the remarkable results in the treatment of cyanide poisoning by the use of intra venous sodium thiosulfate and sodium nitrite received special attention

Treatment of Diabetic Emergencies

Dr McKeen Cattell The subject of our conference today is the treatment of diabetic emergencies Dr Tolstoi will open the discussion

Dr Edward Tolstoi Too much insulin and too little insulin are the chief causes of medical emergencies in the diabetic patient The overdosage and the insufficient dosage may be absolute or relative Too much insulin leads to hypoglycemia, too little, to keto acidosis

Absolute overdosage of insulin denotes the actual administration of more insulin than is necessary This situation is observed most commonly during the initial phases of the treatment of diabetes Some physicians are eager to clear the patient s urine of sugar and consequently either prescribe progressively larger doses of insulin at diminishing intervals or reduce the food intake While such a procedure may clear the urine of sugar, symptoms of hypoglycemia may also develop Some of the patients so treated may be restless at night and complain of headache on arising, or have a feeling of nervousness, weakness and possibly vertigo These are symptoms of slight insulin overdosage Absolute overdosage may also result from a misunderstanding regarding the measurement of the insulin To avoid this it is wise to use a proper insulin syringe, one calibrated to correspond to the unitage of the insulin used A change from the 40 unit strength insulin to the 80 unit insulin is often confusing for the patient, particularly so, if the old 40 unit syringe is used If all details are not carefully explained and demonstrated, he may take double

the prescribed quantity, and, as a consequence, experience an insulin reaction

The treatment of the patient with slight insulin reaction is simple A patient receiving protamine zinc insulin or a mixture of the protamine and the regular insulin, who on arising has a headache, is inattentative, or reveals other abnormal behavior, or who just does not feel himself, although he has no tangible complaints, and who, in addition, finds his urine to be sugar free, is probably having an insulin reaction He should take some orange juice at once and follow it with his usual breakfast The disappearance of symptoms in these cases is not as dramatic as it is in those due to regular insulin I have observed the persistence of symptoms for one or more hours After the symptoms have subsided, the patient may feel a bit fatigued, but as a rule he can attend to his duties As an added safety measure, some food between breakfast and lunch is advisable The other step is obvious Reduce the insulin dosage Do not aim at sugar free urine in the patient treated with protamine zinc insulin A 1+ or 2+ morning glycosuria is acceptable even by the most conservative observers The specific instructions to the patient for the prevention and treatment of such insulin reactions are

1 Take 200 cc of orange juice at once
2 Follow by the usual breakfast which may include additional fruit juice
3 Take a glass of milk and 3 crackers two hours after breakfast

In addition, the physician should observe the following rules

1 Be certain that the patient understands how to measure the dose of insulin
2 Reduce the insulin dosage by 5 units every 3 days until [illegible] the alterna[illegible]
3 Be sure that the patient takes a glass of milk and 3 crackers at bedtime

Relative insulin overdosage may assume different forms, but if one is aware of it as a possibility, its recognition is not difficult Unusual activity is a predisposing cause A gastro-intestinal upset especially with vomiting is another Let me relate some cases A young woman who follows the daily rou tine of a university student, whose diabetes is well controlled with 30 units of insulin and whose diet is generous is invited to a week end party During the day there are ice sports with much skating during the evening considerable dancing She takes a substantial dinner, but omits the crackers and milk at bedtime During the night, she is aroused by her roommate who hears her breathing quite heavily The patient is per spiring profusely and is somewhat confused In this case how ever, she has sufficient presence of mind to ask for orange juice This is taken and is followed by chocolate, milk, and bread Her symptoms abate and after some 3 hours of dis-comfort, she falls asleep On awakening her morning speci men does not contain any sugar in spite of all the carbo-hydrate she consumed during the night This is a classical example of relative insulin overdosage created by unaccus tomed activity Fortunately in this case the diabetic knew what to do, was sufficiently conscious and could retain food which is the very best antidote for an insulin reaction In similar situations give readily available carbohydrate, such as orange juice and other sweets, at once After 15 to 30 minutes, follow this up with milk, bread or crackers This will furnish not only additional, but also a more slowly absorbed, carbohy drate, as a substrate for the insulin Here is another example of relative insulin overdosage A patient takes his morning in sulin, and then for some reason which may not be related to the diabetes he vomits his breakfast Appreciating his need for carbohydrate he tries orange juice repeatedly but finds that he cannot retain that either He needs the help of his physician, since it is obvious that, under these circumstances, carbohy drate will have to be given by another route to prevent the

insulin reaction If the urine contains sugar, it suffices to start with an intravenous infusion of 1,000 cc of 5 per cent glucose Should the urine be sugar free, an additional 50 cc of a 50 per cent glucose solution should be infused The patient s urine must be examined frequently, but as long as glycosuria is present without any other symptoms of diabetes, no additional treatment is required In many cases, if no food is ingested, the vomiting ceases in 24 hours, and the former regimen may then be resumed An emergency of this type is best treated in a hospital

It is obvious that the emergency caused by relative insulin overdosage should be prevented, but when it occurs it should be treated in its earliest phases If unusual activity is anticipated, such as a dance, golf tennis, riding or swimming reduce the morning dose of insulin by 10 units and in addition, advise more food than usual after the activity

A most terrifying emergency is the profound insulin reaction, absolute or relative, which is associated with partial or complete loss of consciousness While this condition can also be treated at home, the patient is far better off in the hospital The most effective measure is glucose given intravenously It should be given continuously, either as a 5 or 10 per cent solution, until sugar appears in the urine Clinical signs of recovery appear slowly and may not be very impressive for hours after the appearance of sugar in the urine Careful observation, however, will reveal encouraging signs The patient may respond to such simple requests as to move an arm or leg, and he may also attempt to take fluids by mouth when they are offered Not infrequently during the comatose period one finds acetone but no sugar in the urine Under no circumstances should insulin be given One must not be misled by the finding of acetone, for it may be a result of starvation If there is no sugar in the urine, there is the indication for glucose, orally, parenterally, or by both routes If the hypoglycemic syndrome is caused by an overdosage of regular insulin,

a subcutaneous injection of 1 cc of epinephrine (1 1 000) may revive the patient sufficiently to enable him to take fluids by mouth The response to epinephrine in cases in which protamine zinc insulin has been used however, is not satisfactory Quite the contrary, the epinephrine may aggravate the ketonuria and further complicate the picture

The emergency arising from too little insulin is more serious It is due to keto-acidosis and may result in coma The insulin insufficiency may be absolute or relative Absolute insulin insufficiency occurs during the course of the disease if it is not treated or in the diabetic under treatment who fails to take the insulin systematically He may omit the insulin because of spitefulness or capriciousness he may have broken his syringe, or needle, or he may have used up his supply of insulin It may seem incredible that the administration of insulin is discontinued for such reasons but it, nevertheless, does happen Some patients pay dearly for their carelessness by the development of diabetic acidosis But somehow, some of these patients cannot or do not wish to learn or profit by their experience Such lapses occur even though the physician has taken all the necessary pains to impress upon the patient the view never to discontinue insulin unless so advised by him

Relative insulin insufficiency may also be caused by infections and such complications as hyperthyroidism, acromegaly, and Cushing s syndrome I use the broad definition for the latter term in which the adrenal gland may also play a role With the development of any such complications, the efficacy of insulin is reduced and consequently, a dose which may have been sufficient previously now becomes inadequate The resulting keto-acidosis may be mild, moderately severe, or severe

THE MILD CASE The trained diabetic patient under observation will usually feel well maintain his weight and carry on free of symptoms and although he may have glycosuria,

4 If fluids cannot be taken by mouth give a rapid intravenous infusion of 1,000 cc of 5 per cent glucose in physiologic saline at once After that, and until the oral route can be used, infusions are continued at a slower rate Care must be exercised to prevent overloading the heart, especially in the case of older diabetics with arteriosclerosis or in those known to have heart disease

5 After the urine has become free of acetone, continue 25 units of insulin and 2 glasses of orange juice every 2 hours for 4 or more doses

While other plans may be advised elsewhere, we have used this one with eminently satisfactory results during the last 15 years

Dr Cattell Dr Tolstoi is ready to answer questions or receive comments on the plans for the treatment of emergency disorders occurring in connection with diabetes

Dr Harry Gold Did I understand Dr Tolstoi to say that in diabetic acidosis, he uses infusions of sodium chloride solution?

Dr Tolstoi That is correct

Dr Gold Does he ever use a solution of sodium lactate instead of ordinary physiologic saline, and if so, when and how much?

Dr Tolstoi We sometimes use sodium lactate but it is not part of our standard routine I think we do just as well with the saline and glucose In the patient with keto acidosis I believe that the most important agent is insulin next in importance is fluid Since the total dose of insulin is large in these cases, the use of glucose ensures against the patient passing from diabetic acidosis to hypoglycemic shock

Dr Cattell You do not think it necessary to correct the acid base disturbance directly, is that it?

Dr Tolstoi We do not We have not had much difficulty due to disturbances in electrolyte equilibrium, Dr Cattell The cause of diabetic acidosis is the production of excessive

amounts of ketone bodies They are excreted, in part, in combination with ammonia the production of which is increased and in part in combination with fixed base thus drawing on the body stores of base If we reduce the production of ketone bodies we have a means of controlling the acidosis The overproduction of ketone bodies takes place when the diabetes is not under adequate control In this state the body metabolizes more than the usual amount of protein and fat There is experimental evidence which shows that if ketone bodies reach let us say 60 or 70 mg per 100 cc of blood 50 Gm of glucose given intravenously will by itself reduce the ketone bodies to 30 or 40 mg per 100 cc The combined use of insulin and glucose increases the rapidity of glycogen deposition in the liver

Dr Cattell Are there any occasions when you believe you must treat the acidosis directly because the blood pH is so low? Don t you prefer bicarbonate any more in such cases?

Dr Tolstoi We don t determine the blood pH We use the acetone in the urine as our chief guide to therapy and the progress of the disease

Dr Cattell But you did use sodium bicarbonate some years back?

Dr Tolstoi Yes I know In the pre insulin era for the diabetic in acidosis we did use bicarbonate We were never quite sure whether it did any good and in the treatment there was a great deal of vacillation When such a patient received bicarbonate of soda and died we would say We will never use bicarbonate again Then came along the next patient in whom the bicarbonate was withheld and when he died in acidosis we found ourselves saying We ought to have used bicarbonate

The advent of insulin has changed the situation Now the vast majority of these patients recover However, we still encounter cases of keto acidosis associated with shock and anuria In 2 or 3 such cases we sought the advice of Dr Van

among the adaptive mechanisms the fixed base or the sodium *in the blood is called* upon so that the bicarbonate level of the blood falls The loss of sodium base leads to diuresis and dehydration, and excessive dehydration may lead *to* circulatory and renal failure The administration of in fusions of sodium chloride would seem to be the proper method for restoring blood volume and extracellular fluid, and *in* that way correct the circulatory failure which may have been responsible in part for the breakdown in renal function This should have the further effect of lowering the acidosis, because one of the functions of the kidney is to produce ammonia for the maintenance of acid base equi *librium, and* a *kidney in which the circulation is greatly* impaired may not be in a position, among other things, to produce enough ammonia The use of sodium chloride infusions would, therefore, seem to be an indirect method, although a vital one, for correcting the acidosis However, I wonder whether this may be enough in the more advanced cases, and whether in these an additional supply of base without a strong acid ion, as would be the case through the use of sodium bicarbonate or sodium lactate, might not be helpful in counteracting the damaging effect of the acidosis per se by direct neutralization of the acid, and thereby save some of those cases which are lost when treated with saline infusions alone I know of no method for counteracting the specific toxic effects of excessive acetoacetic acid

Dr Tolstoi We have treated patients with *CO_2 com bining power* as low as 5 volumes per cent a state of pretty deep acidosis, although not necessarily one producing un consciousness, with salt alone, in addition to insulin and glucose, and they have recovered On the other hand, I can recall the case of a patient who was *unconscious* for 10 or 12 hours and who died despite the fact that he received salt, sodium lactate, blood, and all of the adjuvants we know, in addition to usual doses of insulin and glucose Theoreti

cally you may be right, Dr. Gold. Your explanation is attractive, but practically it works out that, if the patient is conscious, we need use nothing but insulin, glucose, and salt. In the discussions on the need for glucose there has been a good deal of heat but very little light. As I stated, I think insulin is the most important agent. The fluid and what it contains are of lesser importance. I have not had enough experience with lactate, however, to argue for or against it.

Dr. Cattell: If the patient's kidneys were not functioning at all, the sodium chloride would have little effect in directly overcoming the acidosis, because the chloride and the sodium base would be retained.

Dr. Gold: As I stated, the sodium chloride infusions might still be effective indirectly, because, by correcting the dehydration, renal function might be resumed.

Dr. Tolstoi: When there is anuria due to blood pressure falling to shock levels, the patient's chances for recovery are very poor indeed. I think both Dr. Cattell and Dr. Gold have presented a sound argument from a theoretic point of view. However, when these patients are treated in the way I have outlined, the results are very satisfactory. In a 5-year period, 100 cases were treated in this hospital, chiefly by the house staff, not by a team of specialists. They did a fine job. Among the 100 cases, there were 7 complicated by other conditions which could have caused the fatal outcome, namely, *meningitis, acute coronary closures, intestinal obstruction*. There were only 2 deaths due to the acidosis per se. One of those was a patient with unusual resistance to insulin, who required several thousand units of insulin daily to abolish the acetone; the other was one who entered the hospital after being unconscious some 10 or 12 hours. She had been treated by a Christian Scientist and then, when the situation got out of hand, she was brought here. All cases were treated principally with insulin, saline, and glucose. In

those in whom the situation appeared desperate, however, blood and sodium lactate were used as well

Visitor It seems to me that Dr Gold has made out a much better case for the use of sodium bicarbonate than for sodium lactate Is it not true that good liver function is required to utilize the lactate and thus to make sodium available to the patient? It would seem to me, therefore, that in a desperate case, it would be advisable not to rely on the liver and to give the bicarbonate

Dr Gold I would agree with that

Dr N T Kwit In the event that one wished to use sodium lactate or sodium bicarbonate, what doses would one give?

Dr Gold There is a formula for calculating the amount of one sixth molar sodium lactate solution necessary It is based on the value of the CO_2 combining power and weight of the patient However, satisfactory results may be obtained by an intravenous infusion of 30 cc of the one sixth molar lactate per Kg, and repeated if necessary Such a dose may increase the sodium ion concentration of the blood plasma about 7 mm per liter, corresponding to an increase in the bicarbonate concentration sufficient to raise the value of the CO_2 combining power of the blood plasma by approximately 15 volumes per cent The equivalent of this in the form of sodium bicarbonate would be about 0 4 Gm per Kg, or a total of about 25 Gm for the average adult

Dr Cattell I wonder whether we know how important the acidosis per se is among the dangers in this condition Do you consider the acidosis the primary cause of the coma?

Dr Tolstoi I do not know the role of the acidosis per se, it is certainly not the sole factor Consider the case of some patients who come into the hospital in diabetic acidosis and are unconscious The blood picture may be characteristic high blood sugar, low CO_2 combining power, and acetone We have observed the course at hourly intervals in

these, as others have done The abnormalities were corrected The CO_2 combining power would rise to 50 volumes per cent, and the ketone bodies would disappear from the blood and urine, but some of these patients would die There may have been no kidney shutdown Why such patients die I don't know I once asked for an explanation at a meeting of eminent workers in the field, but no one seemed to have any

Dr Gold How do they die? What happens to them?

Dr Tolstoi They just keep on breathing faster and faster, and finally die

Dr Gold Is it circulatory failure, respiratory failure, pulmonary edema, or what?

Dr Tolstoi An hour before death, in a case which I recall very clearly, there were no evidences of circulatory failure A physician was observing the patient most of the time The blood pressure was maintained until about an hour before death We had no idea what caused death in this case Post mortem examinations in similar cases have revealed nothing specific

Dr Seymour H Rinzler May I ask what one does in the case of the cardiac who is in ketosis and in whom sodium is contraindicated because of congestive failure?

Dr Tolstoi Acidosis is a very effective dehydrating factor, and these patients are fairly well dehydrated This can be judged from the high hemoglobin, as well as from the general appearance Congestive failure is, therefore, not a common problem In cardiac patients, I give the fluid very slowly to avoid overburdening the heart In older patients, I sometimes give it subcutaneously

Dr Rinzler Do you not worry about retention of sodium?

Dr Tolstoi No, I don t

Dr Gold Congestive failure is a condition in which there is tissue hyperhydration, too much extracellular fluid Severe keto acidosis of the diabetic is a condition in which there is

dehydration, too little extracellular fluid Theoretically, it should be impossible for the two to occur simultaneously The situation, however, is more complex, for there are occasional cases of congestive failure with severe diabetic acidosis and coma, in which pulmonary edema develops It may be that, in some, even advanced acidosis is not sufficient as a dehydrating factor and that the factors other than dehydration play a more important role in the causation of the coma of the keto acidosis In the few that I have seen, I have relied on the insulin and sugar to correct the acidosis, and on the mercurial diuretic to combat the pulmonary edema even though the diuretic leads to a further loss of sodium *There is, of course, always the possibility of an error* as to the cause of the coma I do not know how to make sure of it These are patients with long standing congestive heart failure and long standing diabetes, who develop coma without clear evidence of a cerebral accident, and in whom one finds a very low CO_2 combining power, a high blood sugar, and sugar and acetone in the urine They sometimes have an azotemia so that one remains uncertain as to whether the coma is caused by uremic or diabetic acidosis

In this connection, another problem might be worth mentioning When renal failure complicates chronic heart disease with diabetes, the patient may develop edema and effusions These suggest congestive heart failure They may however, be the result of the retention of sodium, in the individual whose damaged kidneys cannot excrete enough acid The retention of sodium leads to edema Attempts to treat the edema by mercurials or other diuretic measures, may give rise to mental disturbances, unrest and prostration, which may progress to coma When seen, the patient may present the evidence of diabetic acidosis, renal failure, and coma, and the coma, while due to an acidosis, is not caused directly by either diabetic or renal acidosis, but by the treatment attempting to control the edema, counteracting thereby a pos

sible protective mechanism of sodium (and with it water) retention

Dr Walter Modell How do you treat the diabetic emergency that develops as the result of a serious acute infection?

Dr Tolstoi In exactly the same way as I have outlined Let us say that in a case of pneumonia the diabetic patient s compensation breaks The established routine for the control of diabetes is abandoned We switch from protamine zinc to regular insulin The urine is examined for sugar as often as the patient voids When the test shows 4+, we give 25 units of insulin when it is 2+ or 3+, 15 units of insulin and when the urine is sugar free we give orange juice The pneumonia is treated with penicillin After the infection subsides and the abnormal urinary findings disappear the patient returns to his former regimen

Dr Cattell Can the patient be forewarned about this and be taught to take care of himself in relation to acute infections?

Dr Tolstoi We do that Dr Cattell If the patient has a cold or other infection he knows enough to be on the look out for acetone Life is now very easy for the diabetic patient as well as for the doctor There are powders on the market for testing for acetone All the patient does is to put a little powder on a piece of paper and a drop of urine on it If it turns purple it is positive for acetone in that event, the patient follows the established routine testing the urine until the powder remains white when urine is added In our clinic, when we find acetone in the urine our patients usually know what to do without further instruction

Dr Modell What would you advise a diabetic patient who has suffered a serious burn in anticipation of a break in diabetic compensation?

Dr Tolstoi I would tell him to examine the urine for sugar and acetone and if acetone appears to take regular

insulin in accordance with the plan I have outlined, until the acetone disappears

Dr Cattell You would not ask him to readjust the dosage with the expectation that there was going to be a break in the diabetic compensation?

Dr Tolstoi No, I don't think so at least we have not done it yet It may be a good idea to do that

Visitor Do you believe there is a place for globin insulin with zinc in the treatment of medical emergencies?

Dr Tolstoi No, I do not None of the slow acting insulin preparations should be used in an emergency The only insulin to be used in emergencies, in my opinion, is the regular soluble crystalline insulin, a material which produces its effects quickly One ought not to wait 6 or 8 hours for an effect in a critical situation

Dr Cattell Do you give insulin intravenously?

Dr Tolstoi We hardly ever give it intravenously Once in a while we put 25 units of insulin into a glucose infusion but otherwise it is given only subcutaneously

Dr Greenspan In the case of a patient who enters the hospital with acidosis and severe insulin deficiency which has persisted for some time, might one give somewhat larger initial doses, say, 50 or 100 units?

Dr Tolstoi I am glad you asked that question The initial dose of insulin ranges from 25 to 400 units in different clinics When small doses are given, the intervals are short, and when larger doses are used, the intervals are longer We give 25 units as the first dose, Peters of New Haven gives a 50 unit dose, Olmsted of St Louis gives 100 units, waits an hour and a half determines the blood sugar to see whether more is needed, Rabinowitch of Montreal gives 400 units, 200 units of protamine zinc insulin and 100 of regular insulin subcutaneously, together with an intravenous infusion of 100 units of regular insulin and very large amounts of glucose

Our results are very satisfactory, but that does not mean that our method is superior to that of others There are many factors which may determine the result For example, Owens of Cincinnati, using schedules of 50 unit doses of regular in sulin and careful clinical and laboratory observations as guides has nevertheless, had a relatively high mortality rate This may be explained by the fact that he receives his patients from an ambulance service Such patients are likely to in clude a considerable number who are neglected and who may be in a more advanced state of acidosis with more profound coma than most of ours

Education is important in preventing acidosis We instruct our patients to come to the hospital the moment they suspect an infection or any unusual situation They may even give themselves an extra dose of insulin before starting for the hospital In most of our cases the ketosis disappears in about 6 hours because it is already under control on admission

Dr Greenspan Do you ever use larger doses of insulin than you indicated in your plan?

Dr Tolstoi I do not

Dr Greenspan Do you believe that all emergencies can be managed with only 25 unit doses of insulin?

Dr Tolstoi I do

Dr Greenspan That is a debated point

Dr Tolstoi My own experience leaves me no reason for changing my view I see no objection to using doses of 100, or 200 or even 300 units if one knows the objective I can only say that our very satisfactory results have been obtained with small doses given frequently

Dr George Reader If a diabetic who is controlled with protamine zinc insulin, develops an occlusion of a coronary artery, would that alter the procedure? Would you not change from protamine zinc insulin to regular insulin?

Dr Tolstoi I don t think I would I would just make cer tain that glycosuria is present, and no symptoms of diabetes

I would make no change in the regimen unless there w definite indications, such as ketosis

Visitor I want to ask Dr Tolstoi whether he favors two syringe or the single syringe technic for patients v receive both the regular and the protamine zinc insulin

Dr Tolstoi When one can reduce the number of in tions, one should do it Remember, the year has 365 d When both are necessary, I mix them in one syringe, make only one injection instead of two It spares the pati much discomfort over the years The mixture which I h found most successful is the two to one mixture, 2 parts regular and 1 part of protamine zinc insulin

Dr Gold How would you distinguish diabetic coma fr insulin coma in an unconscious lady in the ladies' room Macy's department store?

Dr Tolstoi The lady in diabetic coma is apt to have a and flushed skin, a fruity odor or the acetone breath, s eyeballs, and a red tongue She may have the typical hunger or Kussmaul breathing Diabetic acidosis devel slowly, and hours elapse before coma develops A person w ketosis so serious as to verge on coma is not apt to be sh ping in Macy s Insulin shock, on the other hand, is enco tered quite frequently in department stores In such a p son the skin is apt to be moist and pale the eyeballs are n soft, and air hunger is absent This person is more apt have twitching or convulsive movements A positive Babins may be present The urine analysis will very quickly discl what the condition is In diabetic coma there will i variably be glucose as well as acetone, while in the case insulin coma, the urine will be sugar free and probab acetone free as well, although occasionally acetone may present, and sometimes even sugar when the bladder co tains urine secreted several hours previously

Dr Gold Would you have any hesitation in proceedi to treat this person with insulin as a case of diabetic a

dosis on the basis of the clinical differentiation you presented, if you were not in a position to examine the urine?

Dr Tolstoi Oh, but I would have to have her urine

Dr Gold But you can t have it

Dr Tolstoi I know that in Macy's I could get a specimen of urine, but if I couldn t, I think that our technic of small doses of insulin adequately covered with glucose is ideal With this procedure one cannot get into any trouble, and one can carry the patient along until it becomes possible to obtain a specimen of urine

Intern Would the blood pressure help in this case?

Dr Tolstoi Not as a rule

Dr Gold Has solution of posterior pituitary any place in the treatment of an insulin reaction?

Dr Tolstoi Yes it is a direct antagonist to insulin, as is epinephrine Both of these are of value in the case of a reaction to regular insulin, but not very effective in the case of protamine zinc insulin

Dr Cattell What is the basis for the difference?

Dr Tolstoi It is due to the difference in the speed of action of the two forms of insulin Regular insulin is rapidly ab sorbed, and its peak effect is prompt The rapid fall in the blood sugar may give rise to an insulin reaction at a time when the level of the blood sugar is still in the normal range It is the rapid change rather than the absolute level of the blood sugar which may cause a reaction in the case of regular insulin Furthermore, in such a case, stores of glycogen may still remain in the liver The epinephrine is effective here because it exerts its action by the release of glycogen from the liver In the case of protamine zinc insulin, epinephrine is less effective, because this form of insulin acts very slowly, and before symptoms of insulin reaction are appreciated the blood sugar has fallen to 30 or 20 mg per 100 cc, and the glycogen of the liver has been exhausted In the absence of liver glycogen, neither epinephrine nor pituitary solution

has any effect on the insulin reaction There is also the fact that protamine zinc insulin remains long at the site of injection, and when epinephrine relieves the insulin reaction in this case, it is likely to be only temporary, because of the continued absorption of the insulin over a long period of time

Visitor Would Dr Tolstoi say something about the preoperative preparation of the diabetic patient?

Dr Tolstoi I think that no diabetic patient need be denied surgery at any time, whether it be an emergency operation or one of election One must make sure of the diagnosis before operation For example, a good many cases of diabetic acidosis present a picture that is difficult to differentiate from acute appendicitis In case of an emergency, before operation, the patient should be given insulin, if necessary, and observed for a little while When there is acidosis, if it is possible it is well to wait until the acetone begins to diminish The patient is taken to the operating room and there given 25 units of regular insulin together with an intravenous infusion of 1,000 cc of 5 per cent glucose in saline As soon as the patient returns from the operating room, another dose of 25 units of insulin together with an intravenous infusion of 1 000 cc of 5 per cent glucose in saline is given If the patient is unconscious, a catheter is inserted, clamped, and specimens of urine are collected every 2 hours If the coma is due to diabetes, the routine which I have already outlined for the comatose diabetic patient is followed In the case of an elective operation, the preparation aims at achieving two results, namely, satisfactory hydration and abundant glycogen storage in the liver The hydration is obtained by means of 1 Gm of salt (2 tablets of 0 5 Gm each) followed by a glass of water every 3 hours To secure glycogen deposition in the liver, I usually give a glass of orange juice and 10 units of regular insulin every 3 hours on the day before operation This results in

a glycosuria, but the presence of sugar in the urine is a matter of no concern as long as the patient's needs for glycogen and water have been met.

SUMMARY

Dr. Gold: The conference this afternoon dealt with the treatment of some specific emergencies which arise in the diabetic patient. The chief medical problems requiring urgent treatment in the diabetic patient are due to either too much or too little insulin. The conditions which bring about these two states were considered—such factors as errors in dosage, unusually vigorous physical exertion in a patient otherwise well maintained, acute infections, burns, and gastric upsets. In general, it seems that reactions to excessive insulin are more frequent, they appear more abruptly, and are apt to be less serious than the emergencies due to insufficient insulin. The emergency due to insufficient insulin is apt to develop slowly and insidiously.

The two types of cases often present striking clinical differences. In the reaction due to too little insulin (ketoacidosis), the skin is apt to be dry and flushed, the eyeballs soft, the tongue red, the fruity odor of the acetone breath may be perceptible, and the typical air hunger or Kussmaul breathing may be present. In the reaction due to insulin overdosage, the skin is apt to be moist and pale, the eyeballs are not soft, air hunger is absent, muscular twitchings may be in evidence, and a positive Babinski sign may be elicited. Coma may be present in both cases. The decisive differential diagnosis between the two conditions depends on an examination of the urine for sugar and acetone, and an examination of the blood for sugar and CO_2 combining power. Sources of error in the interpretation of the findings were discussed.

Emphasis was placed on the need for educating the diabetic patient in the matter of diet, dosage of insulin, and examina-

tion of the urine for sugar and acetone, so as to enable him to recognize the reactions in their earliest forms, to take adequate precautions to prevent them, and to take the first steps in controlling a reaction promptly In the case of in sulin overdosage, the essential treatment is the administra tion of readily available sugar in the form of orange juice or parenteral glucose In the case of the emergency due to in sufficient insulin or diabetic acidosis, the essential treatment consists of frequent doses of insulin, glucose, and the adminis tration of salt and water either by the oral or parenteral route The details of the treatment were fully discussed

Several other matters involved in the medical emergencies of the diabetic received attention, namely, differences in the reactions to regular and protamine zinc insulin, the under lying disorders in diabetic acidosis, the mechanisms by which the disturbances may be reversed, comparison of sodium chloride with sodium lactate and sodium bicarbonate in the control of diabetic keto acidosis, the role of low blood potas sium in the cause of disasters, and the preparation of the diabetic patient for operation

Therapeutic Uses of Gamma Globulin

Dr Ralph Tompsett Within the past few years there have been important advances in the preparation and the clinical use of a number of products obtained by fractionation of human plasma (Method 6 of Cohn) Some of these have received fairly extensive trial There is the serum albumin obtained from Fraction V which as you know is used in the treatment of shock hypoproteinemia and edema From the plasma of group specific bloods isohemagglutinins have been isolated and these provide potent materials for blood grouping Another fraction containing fibrinogen (from Fraction I) has been put to use for the local control of bleeding With the fibrinogen fraction there has been prepared the material known as fibrin foam used for local hemostasis in operations on the central nervous system and the cellophane like material known as fibrin film employed as a dural substitute Fraction I has also yielded a globulin material which is presumably deficient in patients with hemophilia It lowers the clotting time in these patients and is known as the antihemophilic globulin which may be particularly useful in patients with hemophilia who have to undergo surgery

The product from human plasma which has been most extensively used is the gamma globulin a protein obtained chiefly from Fraction II and containing the immune bodies against infectious disease The applications of gamma globulin form the subject of the conference today Dr Alfred Yankauer will open the discussion

Dr Alfred Yankauer From the number of cases of measles

reported to the Health Department this year (1948), we know we are approaching the peak of a moderate sized epidemic Although not as large as the record breaking epidemic of 1941, it will probably be the largest one since then Gamma globulin, also called immune serum globulin (human) is the most useful prophylactic material available to prevent or to modify measles This substance is to be differentiated from the one called 'human immune globulin," which is the old type of human placental globulin

Gamma globulin came into widespread use following the American Red Cross Blood Donor Program during World War II, and the development by E J Cohn at Harvard of large scale methods for fractionating plasma The gamma globulin is obtained from Fractions II and III, chiefly from Fraction II It can be obtained from outdated blood, even from blood as much as a year old In fact, preparations separated from frozen plasma four years of age contained antibody titers as high as the material prepared from fresh blood The antibodies contained in gamma globulin are concentrated about 25 times in the process of separation from plasma Because the pools of adult plasma are obtained from large numbers of donors, the antibody content is quite constant from lot to lot, although some interesting variations do occur After the influenza epidemic in 1943, it was noted that the antibody titer against the influenza A virus rose in the lots of plasma obtained all over the country It has also been shown that antibodies are present in the blood of Easterners against the virus of Eastern equine encephalitis but not against the Western strain

At the present time the material in use is not pure enough for intravenous injection and must be given intramuscularly One must make sure the material does not get into a blood vessel It is best given with a large needle, 18 to 20 gauge The large needle is used because the material is so viscid that it sticks in a smaller gauge needle

Reactions to gamma globulin are conspicuous by their ab-

sence They occur in less than 1 per cent of cases and usually consist only of mild local tenderness A few systemic reactions consisting of mild fever for a day or two have been reported, but these have been encountered in less than 0 25 per cent of the cases

Gamma globulin has the interesting property of inhibiting the action of complement *in vitro* This inhibition can be reversed by the addition of serum albumin to the mixture It does not occur *in vivo* In humans very large doses have been used with no effect on complement This is a property which is of no practical significance at the present time, but may prove to be of some significance if a preparation suitable for intravenous injection comes into use

I would also like to point out that the cost of manufacturing gamma globulin is very high, and the administrative difficulties entailed in securing a supply of it are tremendous Its general use as a prophylactic agent presents problems of quite a different order from that of penicillin or the sulfonamides It is very expensive It is obtained only from humans

The principal use for this material in medicine at the present time is to prevent or to modify measles There have been many extensive and very well-controlled studies which indicate that gamma globulin is a valuable and effective agent in preventing or modifying measles It is well to prevent measles in all very young children and also in some older children or adults under special conditions such as in states of general debility, pulmonary tuberculosis or other diseases, or in patients in hospitals who might present a hazard to other patients *Prevention of the disease, however, also prevents the* individual from developing an immunity of his own as protection from further attacks For this reason, it is our object in older children generally, only to modify the measles, not to prevent it There is the borderline group between the ages of 3 and 5 years in which the decision as to whether to modify or prevent the measles, is a matter of individual judgment

In those over five, one should certainly attempt to modify the disease rather than prevent it completely

In the early studies with placental globulin and convalescent serum, it was thought that an important factor determining the effect of the dose was the lapse of time after exposure It was believed that if the agent was given soon after exposure to measles, it would prevent the disease, if given late, around the seventh or eighth day after exposure, it would modify the disease Studies with gamma globulin, however, have shown clearly that this is not important in determining whether the disease is prevented or just modified The deciding factor is the dose It may be given any time before the eighth day after exposure, and it will either prevent or modify the disease, depending on the dose A dose of 2 cc of gamma globulin, the contents of the standard vial now available, will prevent the disease in approximately 95 per cent of exposed, susceptible household contacts under the age of one, approximately 80 per cent in the ages of one and two, 70 per cent in the ages of three and four, and 60 per cent in the ages of five and six I should emphasize that these results are not from exposures at school or other casual exposures of one sort or another They are obtained from individuals who are susceptible to measles and who have been intimately exposed at home

The dose of gamma globulin used for the prevention of measles is 0 2 cc per Kg , and the dose required for the modification of measles is 0 04 to 0 05 cc per Kg It is convenient to remember the dosage in terms of the standard 2 cc vial In general, a dose of 2 cc prevents the disease in the age group in which measles should be prevented, and modifies the disease in the older group in which measles should be modified

I would like to point out that modified measles is a disease essentially different from regular measles The incubation period may be lengthened, the disease is milder, and many of the ordinary signs of measles may be absent The duration of the immunity from gamma globulin is no longer than two or

three weeks and may be less It is very difficult to know the exact duration of the immunity because multiple exposures are so common When loss of passive immunity is indicated in a given child by the development of measles, it is often impossible to tell which exposure was the cause of the disease

Thus far, I have discussed the use of gamma globulin as a prophylactic following the exposure to measles Before we proceed to the consideration of other uses, it should be mentioned that in the treatment of measles gamma globulin is of no practical importance

Acute infectious hepatitis is another disease in which gamma globulin has proved useful Extensive studies in the Army and a number of studies in institutions have been reported These leave little doubt that gamma globulin is effective in preventing acute infectious hepatitis In control groups, 8 to 12 times as many individuals developed acute infectious hepatitis as in those exposed in whom gamma globulin was used The doses have ranged from 0 12 to 0 3 cc per Kg In one study in adults, a standard dose of 10 cc proved quite effective Again, this agent has no value in the treatment of this disease, once it has developed

The use of gamma globulin in the prevention of acute infectious hepatitis should be differentiated from its use in attempts to prevent homologous serum hepatitis We have no evidence that gamma globulin itself spreads homologous serum hepatitis It has been used in an attempt to prevent this disease in some extensive Army studies involving about 6 000 individuals who had been given blood transfusions Doses of 10 cc had no effect in preventing the disease It did seem to lengthen the incubation period After larger doses namely, 20 cc given in 2 fractions, there was some indication that it might prevent the disease, but in the particular study in which this observation appeared there were not enough cases to make it statistically significant In any case, this matter is probably of no practical importance, because it is not feasible

to give gamma globulin to everyone who receives a transfusion

The available preparations of gamma globulin are of no value in the prophylaxis of mumps Moreover, even large doses of gamma globulin are of no value in the treatment or prevention of mumps orchitis However, gamma globulin prepared from the plasma of patients convalescing from mumps has apparently been partially effective in preventing mumps orchitis The 20 cc dose of gamma globulin from patients convalescing from mumps, incidentally, was equivalent to about 4,000 cc of normal adult plasma

Gamma globulin has been shown experimentally to act in scarlet fever in the same manner as scarlet fever antitoxin or convalescent serum Large doses have to be used At present, it is not of practical importance in the prophylaxis or treatment of this disease

In pertussis gamma globulin from normal individuals is of no apparent value, but the gamma globulin from hyperimmune pertussis serum is useful in the treatment and prevention of whooping cough, when it is used in the same way as hyperimmune serum The material is prepared by fractionation of the plasma from previously hyperimmunized donors It is on the market at the present time, although it is still expensive

In experimental animals, human gamma globulin has some effect in the prevention of poliomyelitis, but it has never been tested prophylactically in man It is probably impossible to do so, since it would have to be used in very large numbers of people and the doses would have to be repeated throughout the summer months to make sure of the effect In one well controlled study, its use in the preparalytic stage of poliomyelitis was found to be without value

German measles has achieved notoriety in recent days because of its apparent effect on the fetus of the pregnant woman We have no published reports on the use of gamma globulin in German measles We are familiar, however, with its use in

a few small institutional outbreaks From the results in these, we are doubtful of its value in the prevention of German measles The same applies to chickenpox Here also, we are familiar with a few outbreaks in which it did not seem to be very effective in the dosage used It has been tried in epidemic diarrhea of the newborn, both prophylactically and therapeutically, with no effect A trial has also been made in an influenza outbreak in a children s institution With the dosage used, no effect in preventing or modifying the disease was noted It was tried therapeutically in an outbreak of upper respiratory infection of unknown cause in a large institution, but without effect Finally, I should mention that the material has been given to premature babies without noticeable effect on the regaining of birth weight, on mortality, or on any of the other factors that were measured

In summary, gamma globulin has two important uses first, as an agent for preventing or modifying measles, and second, for the prevention of acute infectious hepatitis in institutional outbreaks The New York City Health Department gives the material to physicians who desire it for their patients under 5 years of age who are household contacts of cases of measles The Health Department also provides it for patients above the age of 5, if the physician thinks there is some special reason for protecting the particular individual In addition, it may be obtained for use in institutional outbreaks of measles and certain other special situations

Dr Tompsett There must be many questions you want to ask Dr Yankauer The mechanism of action of the gamma globulin is of a good deal of interest What is known about the antibody content of the material? Despite the effectiveness of gamma globulin in the cases Dr Yankauer has mentioned there still seems to be a little bit of black magic about why it works The amount of antibody added to the patient s normal supply by the usual dose of gamma globulin seems to be so small Can anyone tell us about the antibody

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Dr Yankauer I would agree with that

Dr Tompsett Are there other questions?

Dr Walsh McDermott I would like to ask Dr Yankauer about the gamma globulin obtained from the serum of persons convalescing from mumps First, is it available in commerce, and, second, is it of any value for the prevention of orchitis, when given after the parotitis has become evident?

Dr Yankauer The material is not available in commerce It was manufactured just for a specific study It prevents orchitis, if it is given within the first 24 hours after the parotitis has developed

Dr McDermott How much mumps convalescent serum would have to be administered to obtain the same effect?

Dr Yankauer The dose of gamma globulin from serum of convalescent patients was 20 cc, and, since the antibody of the serum is concentrated approximately 25 times in the gamma globulin, the dose of the serum would be 500 cc

In mumps, as in measles the use of large doses of convalescent serum has yielded equivocal results Some studies reported favorable results in preventing mumps orchitis and some in preventing measles I think the answer to the problem lies in the matter of dosage Another aspect of this may be cited

There has been one study of measles reported, in which very large doses of gamma globulin given early in the course of the measles but before the rash seemed to have some effect in modifying the disease It is very difficult to evaluate this result, of course and only the one study has been made The possibility of such use of gamma globulin was known from the observation that large doses of convalescent serum, given early after measles had developed, apparently modified the course of the disease

Dr Tompsett Are there any other questions?

Visitor It was mentioned that modified measles is a differ

titers? The particular disease in which gamma globulin is most helpful is the one in which it is especially difficult to measure antibodies How much do we know about that, Dr Yankauer?

Dr Yankauer There is no way of measuring the titer of measles antibodies

Dr Tompsett In connection with gamma globulin, what antibodies are measured?

Dr Yankauer The titer of mumps antibodies has been used a great deal There are others, including scarlet fever antitoxin, diphtheria antitoxin, streptolysin, and fibrinolysin I think the antibodies against influenza and poliomyelitis have also been measured I can cite more specific data on mumps antibodies The titratable antibodies against mumps virus are 10 times as high in convalescent serum as in normal serum (adult pooled serum), and 25 times as high in gamma globulin as in adult pooled serum Whether this measures the factor responsible for the therapeutic result when gamma globulin is injected is another question, and I don t think we know the answer There may well be other important factors in gamma globulin which cannot be measured in the laboratory

Dr Tompsett That is also my thought Even a large dose of gamma globulin, namely, 10 cc , which would represent the antibody content of 500 cc of whole blood would only increase the normal person s blood antibody content by about 10 per cent on the basis of the data you cited in connection with mumps This would amount to 10 times as much, or doubling of the normal person s blood antibody content, if the 10 cc of gamma globulin had been obtained from convalescent serum We do not know what antibody titers are necessary for protection, but, since such increases in antibody content are not particularly striking it appears to me that some factors other than the added supply of antibodies might play a part in the therapeutic results

Dr Yankauer I would agree with that

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Dr Tompsett Are there any other questions?

Visitor It was mentioned that modified measles is a differ

ent disease Is the danger of post measles encephalitis decreased in measles modified by gamma globulin?

Dr Yankauer I believe that no such complication has yet been reported in a case of modified measles I do not know of any cases of encephalitis after measles that had been modified I would like to hear about it if anyone knows of such an occurrence

Same Visitor Do you believe that gamma globulin, if given early after the development of symptoms of measles, would prevent encephalitis?

Dr Yankauer I don't think there is enough experience with the material to be able to answer that Encephalitis is quite a rare complication, although a very serious one

Dr Tompsett There is every reason for believing that nonmodified measles confers immunity against that disease However, when the disease is altered as it is in modified measles, there arises the question whether the immunity is not also changed I wonder if Dr Stimson can throw any light on that

Dr Philip Stimson Regarding the immunity resulting from modified measles, I think the consensus is that, if there is enough measles to give a rash, the patient will develop a protective immunity If the modification of the measles is carried so far as to eliminate the rash, the patient does not secure full immunity

There are two other points which I would like to bring up One relates to the indications for modifying measles The Board of Health states in effect We will supply the gamma globulin for children up to 5 years old, and for such patients over 5 as the doctor thinks need it " It is my opinion that every susceptible person, without exception, who is known to be exposed to measles, should be given at least a modifying dose of some form of protective medication The second point relates to the preparations Among the various concerns who supply so called gamma globulin, there are some

who mix it with placental extract Do you know how we can distinguish these products from those which contain only gamma globulin?

Dr Yankauer I am sorry I cannot answer that

Dr Tompsett Dr Stimson, you brought up one point which, while it may be of no great importance to the practicing pediatrician, is very important to those in the home with a case of measles In statements regarding the use of gamma globulin for the prevention or modification of measles authors use the term "exposure" They never define it What do you consider to be an "exposure"?

Dr Stimson One must consider as an "exposure" any reasonably close contact, such as in the home or at school, with a child who within 4 days after the contact develops the rash of measles Count back 3 days from the appearance of the rash in the exposing child, and you have the first day in which it was possible for the patient to transmit measles

Dr Tompsett Why is gamma globulin so effective in measles, and not in scarlet fever?

Dr Stimson There is an interesting theoretic explanation Gamma globulin is derived from pooled blood of the general population Ninety per cent of the adults over 20 years of age have had measles but only 10 or 12 per cent have had scarlet fever One might, therefore, expect the antibodies to be in much higher concentration against measles than against scarlet fever Very large doses of gamma globulin may reduce the incidence of complications in scarlet fever somewhat, but the result is not very striking I think that the value of the serum does not lie solely in the antibody titer For example, 10 000 units of scarlet fever antitoxin and 100 cc of human convalescent serum are comparable in regard to clearing up the rash and neutralizing the toxic manifestations of scarlet fever, but the 100 cc. of convalescent serum has far fewer units of antitoxin.

Dr. Tompsett: What is your opinion of the duration of action of gamma globulin, Dr. Stimson?

Dr. Stimson: I would expect it to be protective a little longer than 2 weeks, perhaps up to 3 weeks, since it is in effect a homologous serum. The protection obtained from the heterologous horse serum cannot be counted on for as long as 2 weeks. I have seen diphtheria develop as early as 8 days after a prophylactic dose of diphtheria antitoxin, although that is quite unusual.

Dr. Tompsett: Are there other questions?

Student: What did Dr. Yankauer mean when he distinguished home contacts from school contacts in regard to the dosage schedules of gamma globulin?

Dr. Yankauer: In the studies carried out for the evaluation of gamma globulin in measles, only household contacts were used. That is an important point, because school or institutional contacts have a much lower attack rate. It has been shown that a susceptible individual intimately exposed to measles in the home is much more apt to contract it than one exposed only in school. Also, the spread of measles is more likely to occur in the crowded home with poor hygiene. The National Health Survey showed clearly that measles occurred at an earlier age and spread more extensively through the family in the substandard areas. It was in these families that this dosage schedule was evaluated, but I did not mean to imply that the doses mentioned were for use only on this kind of contact.

Same Student: Is it the usual practice to give gamma globulin to school contacts?

Dr. Yankauer: As I mentioned before, it is the policy of the New York City Department of Health to supply gamma globulin only for household contacts under 5 years of age and for institutional contacts. That would include nursery school contacts, but not children in grade school. This policy is to some extent influenced by the supply. The material is

difficult to obtain. The present supply was secured from the Red Cross during World War II. It is quite adequate at the present time and with the current policies, but eventually it will have to be replenished. The future supply of this material will depend on the national blood bank program of the American Red Cross. The policy is based on the important fact that measles has a high mortality rate in children under 5 years of age. Eighty five per cent of the deaths occur in that age group. Its use is being restricted to the most important group, although the plan to modify measles in all individuals may be a sound one.

Dr. Stimson: Preparations of gamma globulin can be bought in the drugstore nowadays at $2.75 or $3.00 per vial The price has recently gone down.

Dr. Tompsett I telephoned a drugstore today at 3 P.M., and the current retail price quoted to me was approximately $2.25 per cc.

Dr. Yankauer, you mentioned the possibility of protecting an individual against the development of infectious hepatitis Would you give gamma globulin to other members of the family, if one individual in the family developed hepatitis? My understanding of the present status of infectious hepatitis is that it is really not very infectious under ordinary living conditions, although it is quite infectious in Army camps and the like Families want to know whether they should be given gamma globulin when one member develops infectious hepatitis.

Dr. Yankauer It is difficult to be certain of the wisest practice in such cases As Dr Tompsett stated, there have not been many instances resulting from the familial spread of the disease. It is certainly possible for such spread to occur.

Dr. Tompsett We can state, can we not, that the danger of spread within a family is not great?

Dr. Yankauer: It does not appear to be.

Dr. McDermott: I would like to ask another question

about measles It was mentioned that among the patients who have received preventive or modifying doses of gamma globulin some have febrile illness presumed to be measles but without a rash I would like to know how frequently such illnesses are observed I realize the difficulty in making the diagnosis of modified measles What interests me is the possibility that adults may develop measles many times but with a rash only once Is there evidence that measles can be so modified as to occur without a rash?

Dr Yankauer Yes, I would say that there is such evidence Cases of mild illness with fever, conjunctivitis and perhaps a slight cough, but no rash, occur with sufficient frequency at the proper time after exposure, when gamma globulin has been given, that it seems justified to assume they represent modified measles It seems unlikely that they are due to some other virus infection I wonder what Dr Stimson would say to that

Dr Stimson I think it is not an unusual experience to aim for modification and produce so much modification that one is left uncertain as to whether the slight fever is due to measles or to something else

Dr Tompsett Are there any other comments?

Dr Stimson There is one point I would like to stress about the actual administration of gamma globulin One has to inject it within a very short time after loading the syringe because of the tendency for it to stick in the syringe

Dr Tompsett There is a long period of time, let us say during 8 days after exposure to measles, when one can use gamma globulin effectively Is it the same dose whether given on the first or last day of the period?

Dr Yankauer In actual practice, the available period does not extend from the first to the eighth day One usually does not know that a child has been exposed to measles until the exposing child develops a rash Ordinarily, by that time 4 days have passed From the studies with gamma globulin

I would say that the dose would be the same whether given at the beginning or the end of the period in which it is known to be effective

SUMMARY

Dr Harry Gold In one of our conferences on therapy held in 1941, the topic of discussion was the use of human convalescent serum against infectious diseases The object was to confer passive immunity for prophylaxis or for treatment in infectious diseases by the administration of antibodies obtained from humans Human convalescent serum proved to be effective in prophylaxis against measles, in the prevention and cure of scarlet fever, and there was some indication that it might be of value in mumps and whooping cough There were serious obstacles in the way of the general development of this kind of therapy The doses were large, the cost was high, and human convalescent serum was available in only limited amounts and through special sources as in the case of the Manhattan Convalescent Serum Laboratory which was affiliated with the Department of Health of New York City

The conference this afternoon on the uses of gamma globulin is, in a sense, an extension of that subject, in line with the developments which have taken place in the past few years Dr Edwin J Cohn and his collaborators at Harvard Medical School devised a method for the large scale fractionation of plasma It has been found that the protein fraction, termed gamma globulin, in the form in which it was isolated, contains the major portion of the antibodies against infectious diseases The solution of antibodies obtained from human plasma or serum has now become an article of commerce and is readily available at fairly reasonable cost It is provided by several manufacturers in 2 cc vials under the name of "immune serum globulin (human)" It represents an approximately 16 per cent solution of gamma globu

lin containing the antibodies present in normal pooled plasma but in a concentration about 25 times that of the original plasma In the short period of time since the isolation of this material, its utility has been explored in a number of diseases—measles, scarlet fever, mumps, whooping cough, German measles, chickenpox, infantile diarrhea, poliomyelitis, serum hepatitis, infectious hepatitis, and influenza Thus far, it has proved most effective in the prophylaxis of measles and infectious hepatitis There is some indication *that it may prevent homologous serum hepatitis, and that large doses may act in a manner similar to convalescent serum* in the prophylaxis or treatment of scarlet fever

The subject is still in the experimental stage There now exists experience indicating that some specific diseases, in which the gamma globulin prepared from normal pooled serum is not effective, may respond to gamma globulin obtained from the plasma of patients convalescing from the disease Thus, while the so called "immune serum globulin (human)" has not been found effective in mumps, large doses of gamma globulin prepared from the plasma *of convalescent patients have proved effective in preventing* mumps orchitis, and gamma globulin prepared from the plasma of hyperimmunized donors has been found useful in the treatment and prevention of whooping cough

The use of gamma globulin in measles was discussed in some detail The material now available is apparently without value after the disease is established, and its use is restricted to prophylaxis When the material is given at any time between the first and eighth day after exposure, it will either prevent measles or reduce measles to a very mild disease (modified measles), depending on the size of the dose The view was expressed that modification of measles is desirable in most cases since this apparently allows the patient to develop full immunity while passing through a very mild form of the disease, and that the prevention of

the disease is desirable in only special cases, as in very young infants, and under other conditions in which an active measles would give rise to special hazards either to the individual or to contacts.

The discussion also covered some of the details of administration and raised questions concerning the mode of action of gamma globulin. The current material is suitable only for intramuscular injection and is toxic by intravenous injection. The dose for complete prevention of measles is 0.2 cc. per Kg. and only about one fourth of that, namely, 0.05 cc. per Kg., for the modification of measles. Local and systemic reactions occur in about 1 per cent of the cases and are usually mild. An interesting point concerning the mechanism of action was raised, namely, whether the results obtained with gamma globulin are due solely to the addition of antibodies to the patient's blood. There is some indication that the amount of antibodies so added may be too small to account for the protective effects and that some factor other than added antibodies may be, at least in part, responsible for the therapeutic results.

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The use of gamma globulin in measles was discussed in some detail. The material now available is apparently without value after the disease is established, and its use is restricted to prophylaxis. When the material is given at any time between the first and eighth day after exposure, it will either prevent measles or reduce measles to a very mild disease (modified measles), depending on the size of the dose. The view was expressed that modification of measles is desirable in most cases since this apparently allows the patient to develop full immunity while passing through a very mild form of the disease, and that the prevention of

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ing cardiovascular syphilis A history of treatment with bismuth or arsenic, even in small amounts, is often definitive in establishing the diagnosis of syphilis The same is true of the presence of a lesion characteristic of syphilis such as the Argyll Robertson pupil

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An aortic diastolic murmur in the absence of rheumatic heart disease is presumptive evidence of cardiovascular syphilis Hypertension and arteriosclerosis may cause an aortic diastolic murmur, but most experiences are in accord in the belief that aortic insufficiency as the result of either hypertension or arteriosclerosis is rare

Atresia of the ostia of the coronary arteries as the result of syphilis is always a presumptive diagnosis It is to be suspected when angina occurs in a patient with syphilitic aortitis and aortic insufficiency I wish to lay emphasis on the point

that the angina representing coronary atresia is likely to be due to syphilis only when aortic insufficiency is also present This has been our experience in the syphilis clinic of the New York Hospital

Syphilitic myocarditis and gumma of the heart are extremely rare and their diagnosis always remains little more than a suspicion in unusual cases

The chemotherapy of cardiovascular syphilis is a matter of controversy There are two primary questions Does the treatment accomplish any conspicuous beneficial results? Are there important dangers?

Let me state our position at the outset We believe it is beneficial and that the dangers are not significant Our practice is to treat them intensively The plan we pursued previously consisted of 100 intravenous injections of 0 03 to 0 06 Gm of Mapharsen and 100 intramuscular injections of 0 2 Gm of bismuth subsalicylate Now that the more potent antispirochetal, penicillin, is available, we use this In our present experimental schedule of therapy, we give 20 000 units of an aqueous solution of penicillin intramuscularly every 3 hours, or a single injection of 300,000 units (preferably procaine penicillin) every day, for 14 days, and follow either of these schedules with a course of 300,000 units of aqueous or procaine penicillin twice a week for 10 weeks

The decision to employ large amounts of potent antisyphilitic agents was based on the assumption that a low grade infection, such as is found in cardiovascular syphilis, would require large doses of the drugs The choice of the schedule in the case of penicillin was based on the experimental evidence in bacterial diseases, confirmed by Dr Harry Eagle for experimental syphilis, that a continuous level of penicillin was not necessary to achieve therapeutic results

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out satisfactory evidence that the pain was related to the treatment Most syphilologists now begin treatment with full doses of arsenic or penicillin, and ignore the hazard of a Jarisch Herxheimer reaction, which is essentially theoretic. It is certain that one cannot avoid a Herxheimer reaction by beginning treatment with small doses, since it has been shown in the case of secondary syphilis that, as soon as the dose becomes sufficient to prove therapeutically effective, the Herxheimer reaction may take place

The therapeutic paradox seems to be another bogey At tention was called to this phenomenon originally by the experience that patients with syphilitic heart disease some times went into failure during and after specific therapy If one examines some of the early reports, one finds that some of these patients had heart failure before treatment, that the failure was brought under control, and that they subsequently developed failure again There is no clear proof in these that the specific therapy was anything more than incidental in the course of these events, for bouts of failure with tempo rary periods of recovery are known to occur in other forms of heart disease The notion of the therapeutic paradox has also been applied to the case of aortic insufficiency, and to angina in consequence of narrowing of the coronary ostia There is the possibility that, after specific therapy eliminates the active process, the ensuing scar formation may lead to aortic insufficiency as the result of contracture of the aortic cusps Such scarring at the coronary ostia may also diminish coronary flow It is quite probable that such changes occur The experience in our clinic, with aortic insufficiency oc curring in this way, indicates that it is a benign process with self limiting progression It is our belief that disability from either aortic insufficiency or coronary atresia arising in this manner is essentially theoretic, and that the so called thera peutic paradox should not be used as a basis for withholding specific therapy in cardiovascular syphilis

There is a legend with regard to the nonspecific therapy of cardiovascular syphilis to the effect that treatment with digitalis and other drugs usually called upon in cardiac failure is of little benefit in a patient with syphilitic aortic insufficiency This is quite without basis in fact We have proven time and again in the New York Hospital that patients with cardiovascular syphilis who have gone into failure, respond to digitalis and mercurial diuretics in the same manner as patients with any other type of heart disease

Dr Webster This discussion by Dr Reader has brought up a number of points which are controversial and which will warrant further discussion

Dr Gold, do you have any comments?

Dr Harry Gold I might ask a question or two on some points which I have jotted down What proportion of patients with syphilis who come to post mortem for some reason unrelated to the syphilis show syphilitic involvement of the aorta?

Dr Reader The usually quoted figures concern autopsies of patients who have shown one or another lesion of syphilis In such a group syphilitic lesions of the aorta occur in about 70 per cent In a group of patients with latent syphilis, that is, no manifest lesions of syphilis I believe the incidence of aortic lesions at autopsy would be much smaller

Dr Walter Modell I should like to have this clarified for me I think the statement was made that it was not your intention to keep a sustained level of penicillin, since it had been demonstrated that such a level was not necessary If that is so why is it that doses of penicillin are given every 3 hours in your regimen?

Dr Reader The regimen represents a compromise Dr Walsh McDermott and others have expressed the belief that intermittent doses would be satisfactory, and, in fact, such schedules are being used Most clinics in the country are now using a schedule in which the penicillin is administered for

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about 2 weeks Such a period of treatment seemed to us short for a disease with the type of pathology found in ca vascular syphilis We, therefore, adopted the plan of an i sive treatment for a period of 2 weeks, and extended the ment through 10 additional weeks during which a less i sive dosage schedule is applied

Dr Webster Our therapy is a compromise because w not feel satisfied to discontinue the treatment at the er 2 weeks, on the basis of the histologic evidence Cardiov lar syphilis appeared to be more resistant to arsenical the *than other forms of syphilis* Therefore, we reasoned th might prove more resistant to penicillin We believed we had a greater chance for success by prolonging treat over a period of about 90 days

Dr Gold Is this method which you have just outlined one you advocate for routine use at the present time?

Dr Webster We are using it

Dr Gold You do not give any arsenic or bismuth?

Dr Webster I would not

Dr Gold Only penicillin?

Dr Webster The Veterans Administration and the A have adopted the plan of penicillin for 2 weeks as t therapy for cardiovascular syphilis Similarly in Dr Sto clinic in Philadelphia and in Dr Moore s clinic in Baltim they are treating cardiovascular syphilis with penicillin gi continuously over 2 to 3 weeks

Dr Gold Are the patients ambulant?

Dr Webster Here we hospitalize them for 2 weeks, then carry them on an ambulatory basis

Dr Gold Would you have any objection to having patient receive the injections of the first 2 weeks while h up and about and working?

Dr Webster No

Dr Seymour Rinzler Do you have any statistics on comparison of the results with pencillin and arsenicals?

Dr Webster That question brings up the matter of how to evaluate results in cardiovascular syphilis. The ultimate evaluation is made in terms of the length of time the patient survives after the diagnosis is made, and the nature of the findings at autopsy.

Dr Rinzler Do you have any comparative statistics?

Dr Webster It is still too early for such data.

Doctor What is the outlook for the patient with syphilitic aortic insufficiency from the time of the first bout of failure?

Dr Reader The prognosis varies with the individual patient, and it is impossible to generalize. It depends, in part, on the presence of other heart disease and on the general health of the patient. We have patients in our clinic who have been treated with digitalis and mercurials for 10 to 15 years and who are still gainfully employed. Their work load has had to be reduced. They are not heavy laborers but they are able to support themselves. In general, the prognosis in most cases is now much better than the 1 to 2 year figures which are often quoted.

Doctor Dr Reader, I would like to hear some more discussion on the differential diagnosis of early uncomplicated aortitis, that is, how does one decide between syphilis and arteriosclerosis as the etiologic factor?

Dr Reader I have little to add to what I have already said about this matter. I can only emphasize that angiocardiography is extremely valuable as an aid. Calcium deposition in an irregularly dilated ascending aorta in the presence of a positive serologic test for syphilis or a history of antisyphilitic therapy constitutes strong support for the diagnosis of syphilitic aortitis. In contrast, arteriosclerosis rarely affects the ascending aorta and produces little or no dilatation, hypertension produces a regular, fusiform dilatation of the ascending aorta but not of the magnitude of that seen in syphilis. A mistake can be made when the combination of hypertension and arteriosclerosis produces dilatation of the aorta in a patient

with a positive serologic reaction However, the percentage is definitely in your favor if you call every case with calcified and dilated ascending aorta, and a positive serologic test, one of syphilitic aortitis and treat it as such With the present treatment the risk is negligible There are, to be sure, cases of syphilitic aortitis in which none of the foregoing signs are present, when the disease is in such an early stage that the clinical diagnosis cannot be made

Dr Webster We have always acted on the premise that a patient with a positive serologic test and a dilated ascending aorta should be treated as cardiovascular syphilis By the present methods of treatment one would do no harm even if it turned out not to be syphilitic aortitis On the other hand if the condition is syphilitic, withholding treatment would result in irreparable damage We have preferred to lean over backward, and we have treated a few patients in whom treatment was perhaps unnecessary It has been pretty well proved at autopsy that the majority of lesions, the etiology of which seem uncertain clinically, turn out to be syphilitic when the final answer is obtained

Dr Gold I want to ask you about a situation which we encounter not infrequently in the clinics In the typical case, a man 45 years of age with a blood pressure of 160/90, when examined fluoroscopically, shows quite a bulge in the region of the ascending aorta in the P A view, and in the oblique view the bulge is unquestionable The aorta gives the appearance of saccular dilatation The patient has a negative blood Wassermann and a negative history for syphilis The reason I ask this question is that a dilated aorta in hypertensive and arteriosclerotic disease was described as rare earlier in this conference This seems to be one of the most common sources of diagnostic trouble in our clinics namely, the patient with negative serology with hypertension and arteriosclerosis and with a bulging or widened ascending aorta Would you treat such a patient as a syphilitic?

Dr Webster Not with negative serology and without a history of syphilis I think you have to depend a great deal on the history in these cases

Dr Reader Do you do angiocardiograms on these patients Dr Gold?

Dr Gold No

Dr Reader I think Dr Dotter has shown conclusively that it is impossible to ascertain by fluoroscopy alone whether the aorta is dilated A tortuous aorta can simulate a dilated aorta Without angiocardiography one cannot be certain Dr Dotter has proved in several cases in which a diagnosis of saccular aneurysm of the ascending aorta had been made in the absence of a history of syphilis that the aorta was not sacculated but merely tortuous

Dr Gold I am not sure that I could agree that it is difficult to see a real bulge to the right of the sternum and a localized bulge at the beginning of the aorta when the patient is examined fluoroscopically in the P A and oblique views

Dr Reader I think it is quite common to find bulging of the aorta with hypertension because the pulsations are so prominent but an actual saccular dilatation of the ascending aorta just does not occur without syphilis It is practically unknown I am willing to stand on that

Dr Gold I agree that the typical sac is seen only in syphilis but this represents an advanced lesion There is a stage in syphilis of the aorta where all one sees is a slight bulging It is in this stage in which we encounter all the difficulty in differentiating syphilis from arteriosclerosis or hypertension When one sees a large rounded sphere in the region of the aorta the differential diagnosis is not difficult by any method of examination either angiocardiography or simple fluoroscopy In this connection I should mention that fluoroscopy is more satisfactory than the x ray plate In the former examination advantage can be taken of the most favorable angle of rotation in

the oblique positions for disclosing the maximum salient of a bulge

Dr Webster I should like to add a word about angiocardiography in the diagnosis of the cardiovascular disease It has long been recognized that the diagnosis of uncomplicated aortitis is very difficult This is the most important stage of the disease in which to make the diagnosis because it is the stage in which treatment offers the best prognosis Angiocardiography seems to have answered many of our problems We started it with some trepidation because we were afraid of reactions The only complication has been a mild chemical thrombophlebitis which subsides readily *Angiocardiography is the single most important advance which has been made in* a long time in the diagnosis of this disease

Dr Gold Would you tell us how you do it?

Dr Webster The technic is very simple Through a 12 gauge needle which has been introduced into an antecubital vein about 40 or 50 cc of 75 per cent Neo Iopax or 70 per cent Diodrast are introduced into the circulation It is the usual procedure to take two left anterior oblique films The first is *taken in an average of about 10 seconds after the injection of* the contrast medium has begun The interval varies with the cardiac status In the presence of failure the interval is considerably longer The radiologists now have a special x ray machine It takes film at intervals of 0 6 second and as many films as are necessary can be taken The films are larger than the routine chest film to make accurate measurements possible

Dr George Peabody In relation to Dr Gold s point about the diagnosis of early dilatation I think the series of patients which we are now studying may be of some interest In these we obtained a simple chest x ray and an angiocardiogram The angiocardiogram sometimes shows a dilatation which is not seen in the x ray and conversely a contour interpreted as a dilatation in the x ray fails to appear in the angiocardiogram The angiocardiogram has proved to be the only method

of establishing the diagnosis of dilatation with certainty

Dr McKeen Cattell In speaking of the therapeutic paradox, Dr Reader mentioned scarring as one of the complications of therapy Does he have evidence that scarring is less in the same period of time without treatment? Is scarring specifically accelerated by the treatment?

Dr Reader I am not sure of that, Dr Cattell Our evidence indicates that scarring is part of the pathologic process, and it is our belief that it develops even after the inciting organism has been eliminated

Dr Peabody In view of what Dr Reader has just stated, what would be the significance of the serologic test? We have had patients with a diagnosis of uncomplicated aortitis who received treatment which we considered to be adequate and in whom the serologic test turned negative after the treatment Some of these, however, went on to develop aortic insufficiency We raised the question as to whether these should be re treated Additional treatment would not be logical if the progression to aortic insufficiency were simply the result of an anatomic change in consequence of damage previously produced by the active infection Would a positive or negative serologic test after adequate treatment help to decide the issue?

Dr Webster That is a very good point

Dr Reader I believe that these patients provide evidence for the nutritional mechanical mechanism of damage, and indicate that it is not the active invasion of the aortic intima by spirochetes which produces the aortic insufficiency I do not believe that the kind of patient you describe needs to be re treated irrespective of whether the serology has bcome negative or has remained positive The important point in this connection is the fact which you mentioned, namely, that an adequate course of treatment had been given

Dr Peabody I would also like to ask Dr Reader about another point We have recently seen several patients who were admitted to the hospital for treatment of syphilitic heart

disease because, under clinic supervision, they developed an early diastolic murmur The murmur was heard by several observers over a period of 3 to 4 months It was also heard within the first few days following hospitalization Thereafter a controversy arose, many observers were unable to hear the diastolic murmur and disputed its presence Should that be taken to mean that rest abolished the murmur, and that perhaps we are not employing rest sufficiently in the treatment of the patient with syphilitic heart disease?

Dr Reader I think your observation is a common experience Of course, there always remains the possibility that the murmur was there and for some reason was not heard by the particular observer But this has happened often enough to the same competent observers to leave little doubt that the murmur comes and goes Perhaps it can be explained by dilatation of the aortic ring The dilatation would be expected to increase when the heart is put under stress, and to diminish when the stress is removed, with the result that the murmur would disappear Rest is a very important feature in the treatment of patients with cardiovascular syphilis These patients in failure need greater care than those in failure from rheumatic heart disease They must be warned to avoid overexertion, and even moderately heavy labor should be interdicted for the rest of their lives

Dr Gold I wonder whether dilatation of the aortic ring is the best explanation for the observation that the diastolic aortic murmur is heard at one time and not at another The aortic insufficiency is caused by distortion of the valves in such a manner as to make it impossible for them to make a tight closure The audibility of a murmur under these conditions is related to the kind of vibrations which are set up and the latter in turn depend on the speed and pressure of the circulation Changes in these vibrations would be expected to occur with variations in physical exertion In this connection, it is noteworthy that even in the most advanced forms of

heart failure from any cause, physical exertion, which produces marked increase in cardiac and vascular pressure with marked dilatation, rarely, if ever, produces a basal diastolic murmur

Doctor How much penicillin is given in the 10 week period of treatment?

Dr Reader It makes a total of 6 000 000 units This is in addition to the 2 240,000 or 4,200,000 units which are given in the first 2 weeks, depending on which schedule is selected

Dr Webster One may ask whether we are justified in treating cardiovascular syphilis with penicillin at all We know that penicillin is probably the most potent antispirochetal agent in early syphilis We know its value in neurosyphilis and in syphilis during pregnancy It would seem to be a safe conclusion that, if it is so potent against spirochetes in all those conditions, it will prove effective in cardiovascular syphilis For final evaluation, a long term study is necessary Plans for it are now in the making We shall have the definite answer only when the cases which are now being treated have lived out their lives, and data are obtained revealing whether these lives were longer or shorter than their expectancy by other methods of treatment, and also when a certain number have come to autopsy Penicillin therapy has few hazards I think we are justified in using it until some evidence appears to the contrary

SUMMARY

Dr Clarke Wescoe The treatment of cardiovascular syphilis is a controversial subject There is no complete agreement even on such fundamental questions of whether specific antisyphilitic therapy exerts any beneficial effects, or whether the beneficial effects which may occur are offset by the inherent dangers The position adopted by the workers in the syphilis clinic of the New York Hospital, who have devoted a great deal of attention to the problem of cardiovascular syphilis,

now available Another point of interest is the observation that angina pectoris in the patient with syphilis is likely to be an independent disease, unless it is encountered in association with aortic insufficiency In the detection of syphilitic cardio vascular disease, it is of the first importance to ascertain whether the patient has syphilis, and, in this connection, it was pointed out that the high incidence of negative blood serology in cardiovascular syphilis no longer applies to the present-day problems The use of more sensitive tests shows that the vast majority, 98 per cent or more, of cases of cardiovascular syphilis have positive blood serology The experi ence at the New York Hospital, based on the intensive use of specific antisyphilitic measures, formerly arsenicals and bis muth, and now penicillin, as well as the liberal application of nonspecific measures, such as rest, digitalis, and the mercurial diuretics, indicates that there is much in cardiovascular syphi lis which is accessible to control and that the gloomy outlook of the past may no longer apply to this group of patients There is much promise in the routine use of penicillin for the control of cardiovascular syphilis, both in prevention and treatment The final proof awaits the evidence of the long term investigations which are now in progress

was explored in the conference this afternoon Their experience leads them to the belief that intensive antisyphilitic therapy should be applied in all cases of cardiovascular syphilis They recommend penicillin as the therapy of choice and advocate a schedule of 20,000 units intramuscularly every 3 hours around the clock, or 300,000 units (preferably procaine penicillin) daily, for the first 2 weeks, followed by 300 000 units twice a week for the next 10 weeks The defense of this position lies in the proof that spirochetes are active in the aorta of the patient with syphilitic aortitis and, in the observation reported in the literature, that the duration of life from a particular point in the disease was about 4 times as long in cases that were treated as in comparable ones that went without treatment While the dangers of specific treatment in cardiovascular syphilis are recognized, emphasis was placed on the point that disasters are infrequent and that some of the hazards that are stressed in the literature, such as the Jarisch Herxheimer reaction and the so called therapeutic paradox are, for the most part, hypothetic The discussion embraced points relating to differential diagnosis, the pathogenesis of the cardiovascular lesions of syphilis as a basis for understanding what may be expected from specific antisyphilitic drugs, and the use of nonspecific measures in cardiovascular syphilis The experience with angiocardiography leads to the belief that it is one of the most important aids for detecting the type of dilatation of the ascending aorta which is characteristic of syphilitic aortitis The view was expressed that arteriosclerosis and hypertension produce changes in the aorta that are difficult to distinguish grossly from those of uncomplicated syphilitic aortitis, but the point was made that the dilated ascending aorta, in the presence of positive serology had best be considered as syphilitic aortitis, and treated as such, since a large proportion of these prove to be syphilis, and the few in which that does not turn out to be the case are not injured by the relatively innocuous specific therapy which is

syphilis, is the best form of therapy of central nervous system syphilis If early syphilis were adequately cared for, central nervous system syphilis would be eradicated

The evaluation of therapy of central nervous system syphilis must take into account many factors There is, first, the type of disease Other factors are the race, sex, and age of the patient, the duration of the syphilitic infection, the type and amount of treatment previously received, and the type of spinal fluid change

At the present time considerable controversy exists among authorities on this disease as to whether therapy should be evaluated on clinical grounds or on the basis of changes in the spinal fluid It is important to remember that, in the degenerative types of the disease, antisyphilitic therapy cannot be expected to restore destroyed nerve cells For this reason, Dattner and Thomas have stressed the importance of evaluation of therapy on the basis of changes in the spinal fluid Such an evaluation must take into account the following (1) the cell count, (2) quantitative determination of protein, (3) quantitative titration of complement fixation (4) colloidal gold test If the cell count and spinal fluid protein are above normal, they consider the spinal fluid as active In other words the advocates of this view believe that if the spinal fluid cell count and protein content become and remain normal as a result of treatment even though the quantitative Wassermann and colloidal gold curve remain fixed, the process in the nervous system regardless of its type, has been rendered ' inactive and nonprogressive whether or not the patient has achieved any degree of clinical improvement Under such circumstances they consider further treatment useless Conversely, Dattner and Thomas believe that if the cell count and/or protein content of the spinal fluid do not become normal after treatment or if, following a period of return to normal, the values again become abnormal, the patient should be re treated

Treatment of Neurosyphilis

Dr Walsh McDermott The topic of the conference this afternoon is one of the two most important complications of syphilis Up to about 10 or 15 years ago, it was customary to believe that almost every kind of trouble was in store for the patient with syphilis In more recent years, the problems of the patient with syphilis have taken on a different aspect Syphilitic infection, during the early stages, is now looked upon as a benign disease, which causes no serious damage in most individuals In the main, *only two factors now stand* out as serious problems in the infected person, they are syphilis of the aorta and syphilis of the nervous system Of the two neurosyphilis is by far the more important The discussion of this subject will be opened by Dr Webster

Dr Bruce Webster Since the treatment of syphilis of the central nervous system varies with the type of the disease, it is perhaps well to consider for a moment the matter of classification By far the most frequent is the *asymptomatic* variety It is recognized by the presence of a "positive" spinal fluid The symptomatic variety falls into two general categories, the *inflammatory group and the degenerative group* In the inflammatory group, acute syphilitic meningitis and meningovascular syphilis are the most important The degenerative group includes tabes, paresis, and primary optic atrophy It is well to bear in mind that, due to the diffuse nature of the infection, combinations of the above categories may occur in any one individual

I should like to re emphasize what has often been stated, namely, that prevention, by the adequate treatment of early

syphilis, is the best form of therapy of central nervous system syphilis If early syphilis were adequately cared for, central nervous system syphilis would be eradicated

The evaluation of therapy of central nervous system syphilis must take into account many factors There is, first, the type of disease Other factors are the race, sex, and age of the patient, the duration of the syphilitic infection, the type and amount of treatment previously received, and the type of spinal fluid change

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On the other hand, other authorities are not in agreement with the concept of what is referred to as 'treating the spinal fluid and not the patient" Many patients show inactive spinal fluids before treatment, but give evidence of clinical progression of the disease The patient or his family is much more interested in relief of the symptoms and the maintenance of health Unfortunately, this does not always coincide with inactivity of the spinal fluid Both the spinal fluid changes and the clinical status must be considered in evaluating therapy

Time will not allow a detailed discussion of the older methods of treatment of central nervous system syphilis The results of the so called intensified routine chemotherapy with arsenic and bismuth, either alone or combined with fever, are listed in all standard textbooks and may serve as a basis of comparison in the evaluation of the newer forms of therapy Although induced fever has been used for 20 years, authorities are not yet in complete accord as to the value of this measure applied in the form of malaria or artificial fever, in the treatment of central nervous system syphilis

Two of the therapeutic measures which were formerly used should now be of historic interest only, but unfortunately they are not I refer to the so called Swift Ellis method and tryparsamide You will recall that, in the former method, the patient received intraspinal injections of the serum obtained from his own blood drawn about 30 minutes after an intravenous dose of an arsenical It is a surprise to learn that the Swift Ellis method is still used and that a large amount of tryparsamide is still being manufactured in this country

After the report by Mahoney, Arnold and Harris in 1943, pointing to the effectiveness of penicillin in early syphilis, clinical trials with penicillin in the central nervous system forms of the disease were made In a cooperative study sponsored by the National Institute of Health, considerable information has been accumulated in approximately 5,000

cases of central nervous system syphilis in which the treatment was either penicillin alone, or penicillin and fever therapy. The results have recently been summarized in a report to the Council on Pharmacy and Chemistry of the American Medical Association by the Syphilis Study Section of the National Institute of Health, and published in the *Journal of the American Medical Association*, Vol. 136, p. 877, March 27, 1948. Crystalline penicillin G is the product of choice in the treatment of syphilis in man. It is relatively nontoxic. The only reactions, other than those of the Jarisch-Herzheimer type, are allergic in nature and are mild. This fact alone makes penicillin a highly desirable agent in the treatment of neurosyphilis.

The dosage of penicillin which has been used has ranged from 4 to 10 million units given over periods of from 7 to 21 days. In the New York Hospital, we have used a total dosage of 4.2 million units given over a period of 14 days. This was formerly administered in about 25,000 unit doses at intervals of 2 hours, but is now administered as a single daily injection of 300,000 units. When fever was used at all, it was in the form of malaria or artificial fever induced by the diatherm.

Two schools of thought appear to be emerging: One group advocates the use of penicillin alone in all forms of neurosyphilis. The patient is re-treated if, after the first course, signs of relapse appear, either clinical or in the spinal fluid. The proponents of this plan maintain that the results with penicillin alone are better than those with the older methods of chemotherapy, and are at least as good as chemotherapy combined with malaria; and, further, that penicillin possesses the advantage of complete safety from serious reactions. The other group of investigators advocate the use of penicillin alone in the asymptomatic type, and also in the inflammatory type of symptomatic neurosyphilis, but urge concurrent fever and penicillin in the degenerative types, such as tabes, paresis, and optic atrophy.

The fever therapy may consist of the standard 10 to 12 paroxysms above 39 3° or may be the milder course of 6 to 8 paroxysms as advocated by Solomon

There appears to be a general agreement that penicillin alone exerts a profoundly favorable effect in asymptomatic central nervous system syphilis The cell count of the spinal fluid returns to normal in from 2 to 6 months after treat ment The protein is the next to attain the normal level The Wassermann reaction and the colloidal gold tests show return toward normal more slowly In the inflammatory types of neurosyphilis, i e , acute syphilitic meningitis and meningo-vascular syphilis, the results of penicillin therapy equal or exceed those of chemotherapy

In paresis, tabes dorsalis and primary optic atrophy, the results are perhaps more controversial Nerve tissue already destroyed cannot be restored Some of the disagreement among observers may depend on differences in the type of patients Many of the large syphilis clinics deal, in the case of paretics, with patients who are ambulatory and who do not have to be confined or restrained The results with penicillin therapy alone in these have been, on the whole satisfac tory On the other hand Solomon dealing with psychotics in more advanced stages of the disease, may achieve better results with therapy in which both fever and penicillin are used Again, the basis for some of the controversy may be the fact that the patients in the various clinics have not been entirely comparable

Penicillin certainly extends the life expectancy of paretics Many have been able to return to work From the present evidence, approximately 50 per cent show definite improve ment In the others the condition remains unchanged or deteriorates From 6 to 10 per cent succumb despite treat ment

The recent report to the Council on Pharmacy and Chemis-try indicates that the value of adding malaria to the treat

ment with penicillin is inconclusive. As I have stated, the difference in results with and without malaria may depend on the stage of the disease at which therapy is instituted.

Penicillin produces striking relief of some of the clinical symptoms in many tabetics. Data are not yet available as to whether it will permanently arrest the tabetic degenerative processes. But it is generally agreed that penicillin is more effective in tabes dorsalis than arsenic and bismuth. Whether or not malaria will augment the results is still uncertain.

Just as the results of the treatment of primary optic atrophy with chemotherapy and malaria were far from satisfactory, so is the treatment with penicillin and malaria. However, the latter appears to offer the best form of therapy available at the present time.

The policy we have adopted in the Syphilis Clinic of the New York Hospital offers a "middle of the road" plan. We prefer to use, as a rule, 4.2 million units of penicillin in 14 days as the first course of treatment of all forms of central nervous system syphilis, except primary optic atrophy. If the clinical course of the disease or the spinal fluid change progresses unfavorably after this therapy, it is our policy to give another course of treatment with penicillin alone or penicillin combined with malaria, depending on the urgency of the situation and the patient's general condition. In all cases of primary optic atrophy, we have used penicillin combined with fever.

Follow-up at frequent intervals with combined clinical, psychometric, and spinal fluid examinations is essential in order to evaluate the results of therapy in syphilis of the central nervous system.

In conclusion, it would appear that penicillin alone, ir adequate dosage, given over a sufficiently long period o time, is a safe and effective form of treatment in most type of syphilis of the central nervous system. Further evidenc is necessary to determine whether or not the addition o

fever therapy enhances the effectiveness of penicillin therapy in the forms of the disease which are resistant to treatment with penicillin alone

Dr McDermott The conference is now open to questions Dr Wolff, would you care to comment?

Dr Harold G Wolff The symptoms which are most troublesome to the clinician are those which occur late in the course of tabes, when the patient is referred to as a case of "burned out" tabes I refer particularly to the tabetic crisis and root pains, which ordinarily occur in patients whose spinal fluid and blood are normal, and also cases of optic atrophy Is there anything to be said about the management of these difficult conditions? I understand that some cases of optic atrophy are substantially benefited by the use of malaria I am also told that the process is sometimes arrested, and that if it involves only one eye, the other eye fails to become involved What can be said about the effects of malaria in root pains of the tabetic crisis?

Dr McDermott Dr Webster, would you care to speak on these points?

Dr Webster At a recent symposium on syphilis the various forms of therapy for primary optic atrophy were extensively discussed I find myself on the fence regarding the benefit of any therapy for optic atrophy There has always been the hope that the disease can be arrested, but the situation is now becoming one in which those who have had a great deal of experience are growing more and more pessimistic about the results of treatment of primary optic atrophy due to syphilis This was reflected in the recent summary on this subject by the Syphilis Study Section which concluded that there was not enough evidence for a comparison of the results of penicillin and malaria with those of chemotherapy and malaria Our own experience is also inconclusive, but it is by reason of this very lack of conviction that we continue to use malaria in primary optic atrophy

Dr McDermott Does not the evidence show that malaria without chemotherapy is of no use at all?

Dr Webster Yes but I am pessimistic on the effect of any form of therapy of this condition although here and there something seems to happen to make us suspect that the treatment might have arrested the disease

Dr McDermott Did I understand you to say that the course of a tabetic s pains is altered by penicillin?

Dr Webster I might begin the answer by stating that it was our belief that thiamine chloride which we used for a number of years provided distinct relief of symptoms There are however many factors which might enter into such relief namely changes in climate suggestion and others In the presence of an active spinal fluid we believe that penicillin therapy benefits the patient beyond a question of doubt In the so called burned-out individuals with negative spinal fluid there is no satisfactory evidence of benefit

Dr McDermott The situation in tabes is a good example of the fact that the diagnostic and therapeutic aspects in syphilis have advanced far more than our understanding of the disease It is difficult to understand how an antimicrobial agent could possibly affect the pains of tabes because such an agent could exert an influence only on the microbes It is difficult to conceive of an infection lasting 20 years progressing in no other way than to produce bouts of severe pain at long intervals Yet that is exactly what seems to happen I must admit that it is extremely difficult to arrive at a conviction regarding the value of a new agent for the relief of pain in a patient with tabes but I may express my belief that I have never been convinced that any of the agents previously used namely malaria metals or vitamins significantly altered the pain Despite all of these forms of therapy whenever I saw one of these patients approach I felt a strong inclination to turn and run I am inclined to believe that penicillin has somewhat altered the situation

and that this agent does influence these pains, but it is my impression that the effect is not very substantial. I believe you have in your series here patients who have developed gastric crises while receiving penicillin.

Dr. Wolff: What are the current views concerning the role of malaria in these various types of syphilis? Is its effect in any way different from that of raising the temperature by some hot-box method?

Dr. McDermott: That is also an unsettled question. A special immunity factor is a possibility in the case of malaria. However, fever induced by mechanical means produces results difficult to distinguish from those of fever induced by malaria. It is extremely likely that there is no difference in the mode of action.

Dr. Webster: It might be interesting to mention at this point that some benefit is derived from shock therapy and penicillin.

Dr. Wolff: In what group?

Dr. Webster: In paretics.

Dr. McDermott: Are there other questions?

Dr. McKeen Cattell: Have you thrown the arsenicals out entirely in the treatment of neurosyphilis?

Dr. Webster: I would say that there is no question at all of the desirability of discarding tryparsamide. There is so much danger in this drug. Penicillin accomplishes more in a much shorter period of time. I would go further and state that the same applies to other forms of arsenic and bismuth. Penicillin produces little or no toxic effects and is just as effective therapeutically as arsenic and bismuth. Furthermore, there is the important factor of the markedly shortened period of treatment in the case of penicillin. I believe there is now general agreement that it is possible to accomplish as much in all forms of neurosyphilis with the use of penicillin as with arsenic and bismuth.

Dr. Cattell: Do you not use arsenic in this hospital?

Dr Webster No

Dr McDermott Those who still hold to arsenic and bismuth are I believe ultraconservative I do not think there is the slightest doubt that penicillin is more effective than any chemotherapy as a therapeutic agent for syphilis of the central nervous system It was never possible to produce the profound and extensive cerebrospinal changes with the agents used prior to penicillin

Dr Wolff It may shock you to know, Dr Cattell, that in a careful search of the New York Hospital today for an ampoule of neoarsphenamine none could be found

Dr Janet Travell I had the same experience

Dr Webster I m glad to hear that

Dr Cattell Should we take it out of the *Formulary*?

Dr Webster I wrote a letter yesterday at someone s request making that recommendation

Dr McDermott I see no reason for it to be in the *Formulary* because Vincent s infection of the mouth can also be treated better with other drugs

Dr Ralph R Tompsett I wonder if Dr Webster would enlarge on his statement about the Herxheimer reactions? Was he referring to the Herxheimer reactions in neurosyphilis and if so are they dangerous? He also referred to allergic reactions in penicillin therapy Would he say more about these?

Dr Webster The subject of allergic reactions is a fairly large one I was referring simply to the ordinary hypersensitivity reactions which are encountered in some individuals following the administration of penicillin There has been some reference in the literature to Herxheimer reactions in neurosyphilis especially in paretics and to a lesser extent in tabetics A few observers have noted that the lightning pains in tabes are increased during the period of penicillin therapy Others have reported that the degree of psychosis is increased in paretics These observations have not been sufficiently con

firmed, and I do not believe that enough information c
-cerning them exists to decide whether they are the result
therapy or merely coincidental Doctors Moore and Farn
reported a few cases in which a rise in temperature follow
the administration of penicillin to patients with neurosy
ilis but there were no untoward effects and these few m
have been coincidental

Dr McDermott Are you afraid of a Herxheimer reacti
in neurosyphilis Dr Webster?

Dr Webster I am not We have had no such reactic
here It is only fair to state that there are some who holc
contrary view

Dr McDermott I am inclined to agree with you Spi
chetes are necessary to produce the reaction which refle
the killing of spirochetes The reaction is transient I shou
like to stress the desirability of going ahead with the tre
ment It should not be interrupted because of the reactic
The reports on Herxheimer reactions in tabes are in need
careful scrutiny since a true Herxheimer reaction wou
involve the assumption that there are spirochetes in tab

Dr Wolff Would you say something about the publ
aspect of the new treatment? Is there any evidence that tl
intensive preoccupation with the treatment of very ear
syphilis is reducing the amount of neurosyphilis?

Dr McDermott It is too early for a conclusive answer
that question The amount of early neurosyphilis occurrin
as a relapse of infectious syphilis treated with penicillin
treated with other rapid methods for that matter is very sma
indeed If the patients had only one syphilitic infection an
that were treated with penicillin I have little doubt that th
incidence of neurosyphilis would decline However, there
the point that some of these patients have 3 4, or 5 infe
tions of syphilis and how that would affect the incidence c
late neurosyphilis only time can tell

Dr Webster Don t you think we shall have to wait 10 o

15 years, a time sufficiently long to give these patients an opportunity to develop neurosyphilis, before the effect of the treatment on the incidence of neurosyphilis can be properly judged?

Dr McDermott Perhaps it doesn t have to take so long I believe that the patient who is free from neurosyphilis 2 or 3 years after the initial syphilis, and who does not acquire the disease again, will not develop neurosyphilis I think the patient can be assured early in the game, that the chance of developing neurosyphilis is negligible, provided these conditions prevail effective treatment of early syphilis, absence of reinfection, absence of neurosyphilis after a lapse of 2 or 3 years following the initial attack That may not apply to the development of tabes in all cases of syphilis We simply do not understand the conditions which apply to tabes

Dr Webster, would you tell us something about your plan for follow up? How long does one pursue it and what criteria are used?

Dr Webster I might describe the routine we use here We try to see all patients with neurosyphilis treated with penicillin at intervals of a month after their discharge from the hospital We endeavor to examine the spinal fluid at intervals of three months in the first year If the spinal fluid becomes negative and remains so for a year, the intervals between examinations are prolonged On the other hand if the abnormal findings in the spinal fluid remain unchanged, the follow up is made more intensive All patients with syphilis of the central nervous system should remain under observation for life

Dr Wolff I wonder if we could have some more discussion of the laboratory tests as guides to improvement after treatment by penicillin alone, or by combined treatment

Dr McDermott The evidence is fairly good that the abnormal findings in the spinal fluid, namely, increase in cell count, increase in total protein, and the abnormal protein

reflected in the gold curve, disappear with approximately the same speed under treatment with either penicillin or malaria The same is true of the Wassermann test, but modifications of the complement fixation tests have greatly increased their sensitivity For these to become totally negative would frequently take as long as 4 or 5 years

Dr Wolff Do you refer to both blood and spinal fluid?

Dr McDermott I was speaking only of the spinal fluid It is easier to reverse serologic tests of the blood than of the spinal fluid In a long treated neurosyphilitic, it is not uncommon to find the blood serology negative but the spinal fluid quite 'active '

Dr Webster Don't you believe the type of syphilis would have a bearing on this point? Don't you think that the inflammatory types, such as acute syphilitic meningitis and possibly meningovascular syphilis, show improvement in cells and protein of the spinal fluid more rapidly after penicillin than after malaria?

Dr McDermott I am glad you brought up that point It is possible to compare the two agents only in those types in which one or the other is used Syphilitic meningitis has never been treated with malaria

Dr Wolff Could you perhaps sketch on the blackboard the general course of the changes in the Wassermann test during the first few months of vigorous treatment, and also the changes that one might expect in the ensuing 4 or 5 years?

Dr McDermott For example, if one starts with a six tube titer, at the end of one year after completion of treatment, it may go down to four or a little less At the end of 2 to 4 years only a very low titer may remain In this case it is wise to have the tests made by the same laboratory under the same conditions A titer which has become very low may be found positive by one laboratory and negative by another

Dr Wolff I take it, then, that after the complement fixa

tion test has fallen to a 2+, you might allow the patient to carry that the rest of his life

Dr McDermott If the situation in syphilis is compared with that of other infectious diseases the persistence of a positive serology cannot be regarded as harmful When the syphilologist aims at absolute disappearance of the positive serology, he is aiming at a result impossible to achieve in other infections Sociologic and emotional factors associated with the presence of a positive serology provide a strong pressure behind the aim for a negative serology I am sure that as many people are injured by the knowledge that they have syphilis even of an inconsequential nature, as are harmed by the organic changes of syphilis

Dr Webster Don t you think that the longer the patient has had syphilis of the central nervous system the more difficult it may be to reverse the positive serology?

Dr McDermott I do not know whether it is a general rule Your reference to the rapid reversal in the case of acute syphilitic meningitis supports the view However whether a difference would be in evidence in a comparison between for example a disease with a duration of 5 years and one of 10 years I cannot be sure

Dr Webster I have the impression that the reversal of a positive serology is more readily achieved in early than in long standing cases

Dr McDermott That seems reasonable

Dr Webster It is important to bear in mind that in some patients the positive reaction of the spinal fluid cannot be reversed regardless of the amount of treatment As Dr Mc Dermott has pointed out after a vigorous course of therapy the syphilitic process is probably arrested and nothing is to be gained by continuing treatment for the rest of the patient s life

Dr Wolff May I ask another question? Is there any new

information regarding spontaneous reversal of syphilis of the central nervous system?

Dr. McDermott As far as I know, there is none For in formation concerning a spontaneous cure of syphilis we fall back on the report of Bruusgaard about 20 years ago Al though that study fails to meet entirely satisfactory scientific standards, it is a notable contribution It calls attention to the fact that many patients with syphilis are not seriously affected by it

Visitor Is there any information available on the course of syphilis acquired simultaneously with gonorrhea? I refer to patients who acquire both diseases in the same exposure, who receive a few "shots" of penicillin, and subsequently turn up with a positive spinal fluid or positive blood serology

Dr McDermott I have forgotten the exact incidence of this combination, but I believe it is in the neighborhood of 2 per cent Would you know exactly, Dr Heimoff?

Dr Leonard L Heimoff It is from 2 to 4 per cent

Dr. McDermott Among men in the Army with acute gonorrhea who received penicillin therapy for the gonor rhea, 2 to 4 per cent were subsequently found to have in fectious syphilis, presumably acquired from the same ex posure Those represent partially treated syphilitic infections in which the host parasite relationship may have been up set by the penicillin

Dr Heimoff The only difference we observed in these mixed infections was a delay in the incubation period of syphilis It took about a week longer for the chancre to ap pear, it appeared in a month rather than in 2 or 3 weeks There is also the fact that in most of them the chancre did not appear at all, but a positive serology developed in 4 to 6 months, rather than in the more usual period of 3 months We had to follow these cases serologically for 4 months be fore it was safe to discharge them from observation

Dr McDermott In other words, a man treated for gonor

rhea was also observed for a period of 4 months as a syphilitic suspect, is that so?

Dr. Heimoff: Yes.

Dr. McDermott: Was that only the case when the patient had received penicillin?

Dr. Heimoff: Yes.

Dr. McDermott: Dr. Wolff, have you any notion as to how the pains of tabes are brought about? I vaguely recall a patient with some type of tumor, whom you showed us at Grand Rounds about a year ago, in whom you postulated vascular reflexes as an explanation of paroxysms of pain.

Dr. Wolff: Your memory of the case is correct. It was my notion that the tumor, by irritating the sensory root, reflexly produced vasoconstriction in the sensory root. The tumor was pressing more or less continually, but the pain was paroxysmal.

Dr. McDermott: Do you assume a similar mechanism as the cause of the pain in tabes?

Dr. Wolff: That explanation has seemed attractive to me, since the dorsal root ganglion has such a limited capillary supply, about as little blood supply as in ordinary white matter. There is little margin of safety, and any minor vascular derangement might readily give rise to spontaneous discharge of a painful nature. What, in turn, initiates the vascular discharges, we do not know. It may be some minor change in the neighborhood, such as slight edema, which may have nothing to do with the syphilis itself. Yet the faint restriction of the blood supply may give rise to the painful reaction.

Dr. McDermott: That is a very attractive hypothesis to explain such paroxysms of pain in a state of a disease which is more or less constant for years.

Dr. Webster: I think climatologic factors could explain such paroxysms.

Dr. Wolff: I believe so too. A cold day, drafts, cold drinks,

or hot drinks of water set off tic They might act similarly in setting off an attack in a tabetic

Dr Webster After a few bad days, tabetics come flocking in for therapy of some kind

Dr McDermott Have you noticed any increase in the incidence of herpes zoster in tabetics who have been treated with penicillin?

Dr Webster I have not Perhaps Dr Peabody has

Dr George E Peabody I have seen only one case

Dr McDermott Every now and then a patient with tabes develops herpes zoster, particularly after a bad bout of pain Early in the days of penicillin therapy, the frequency of these cases seemed to have increased, and the question arose whether it might be in some way related to an effect of the drug I know of no evidence for it I suppose there is nothing in it

Dr Wolff After a severe bout of pain, trigeminal tic is also sometimes followed by herpes

Dr George Reader I wonder if you or Dr Webster would comment on the danger of malarial therapy in tabes

Dr McDermott I would like to ask Dr Webster to comment on that Perhaps he also wishes to compare penicillin therapy with malarial therapy in neurosyphilis Which is the less expensive and less troublesome to apply?

Dr Webster I believe all agree that there are no serious complications following penicillin therapy, while, even under the best circumstances there is a mortality of 3 to 5 per cent with malarial therapy of central nervous system syphilis There is no doubt of the fact that penicillin therapy is easier to apply Here we are inclined to hospitalize the patients but ambulatory treatment of central nervous system syphilis is feasible, and is being carried out in other places especially with procaine penicillin Ambulatory treatment materially reduces the expense Where possible or where there is reasonable possibility that one form of therapy is as effective as

the other, penicillin is certainly preferable. Which of the two forms of treatment is the more effective is at present the basis of controversy. If penicillin does not turn out to be inferior, the preference for penicillin will be decisive.

Dr. McDermott: How much does it cost for procaine penicillin in the treatment of a case of neurosyphilis?

Dr. Webster: It is about $70 for a course of therapy lasting 14 days. In the ambulatory form of treatment the patient can go on working.

Dr. McDermott: How long would the patient be out of work in treatment with malaria? What would be the cost there?

Dr. Webster: Each treatment with malaria represents an expenditure of several hundred dollars of someone's money. In this hospital I think our average period of hospitalization is at least three weeks in all cases of malaria. Many stay longer. Then there is the period of convalescence. Federal and state health authorities feel very strongly about the disadvantages of long hospitalization. This is why they are working so hard to develop methods of ambulatory treatment.

Dr. Wolff: Is there any danger of serious dysfunction in tabetics during treatment with malaria?

Dr. McDermott: There certainly is. Manifestations of damage to proprioception are distinctly greater when the patient is put to bed. Even with the relatively benign therapeutic malaria which we use, it is quite impossible to keep the patients up and about. They are too weak.

Dr. Webster: Gastric crises are precipitated by malaria. The lightning pains are very severe when precipitated either by artificial fever or malaria.

Dr. Wolff: How about the bladder?

Dr. Webster. In this hospital we have had several individuals who developed cord bladders during malarial therapy. The patient's vascular system is also an important considera-

Management of Thyrotoxicosis

Dr Ephraim Shorr In the past 5 years, two conferences have been held in this institution for the purpose of exploring and crystallizing developments in the management of hyperthyroidism Advances in our knowledge of this problem were sufficiently rapid to make this necessary As I view the past 25 years of thyroid history, which corresponds approximately to the span of my personal familiarity with it, I am struck by the fact that in the period of the first 15 years, an interval of 5 or 10 years between conferences on hyperthyroid therapy would not have been too long, because of the slow advance of basic discovery The disclosure that thiouracil has the property of causing thyroid hyperplasia simultaneously with diminished thyroid activity provided the impetus to one of the most significant developments in the past decade The entire problem of the nonsurgical treatment of hyperthyroidism has come under scrutiny with attention focused not only on the potentialities of numerous thioureas, but also on radioactive iodine for the cure of hyperthyroidism The enlarged perspective afforded the opportunity to consider from numerous angles the relative merits of nonsurgical and surgical treatment of Graves disease

In the conference this afternoon we shall have the benefit of the keen observations and rich experience of Dr Trunnell of the Memorial Hospital and the Endocrine Clinic of our hospital Dr Trunnell will open the discussion

Dr Jack B Trunnell Thyrotoxicosis is a disordered state of metabolism, the cause of which is not known in most cases

There are a few types in which the causes are now known They are not common I shall do little more than name them for, if the cause is known, the treatment is in most instances self-evident

It is almost certainly a fact that the syndrome of thyrotoxicosis is usually caused by overproduction of thyroid hormones in the thyroid gland Whether or not this overproduction is brought about by some physiologic aberration primarily in the thyroid gland or indirectly by overproduction or underproduction in other endocrine glands, is a matter of conjecture Some types of pituitary overactivity, chiefly acromegaly, are often associated with hyperthyroidism The notion that the common garden variety of hyperthyroidism may result from pituitary overactivity has few adherents and is sustained by negligible evidence We occasionally encounter an individual whose hyperthyroidism comes from a bottle The term thyrotoxicosis factitia is applied to it It isn t always easy to establish this diagnosis because, for some strange reason, some of these patients have a strong disinclination to reveal the fact that they have been taking a medication, and direct interrogation often elicits only a firm denial The administration of thyrotropic hormone may bring on hyperthyroidism Another variety of hyperthyroidism is seen in patients with thyroid cancer and metastatic deposits This is very rare The majority of these show no evidence of hyperthyroidism, even cases with as much as two kilograms of metastatic thyroid which has the appearance of functioning tissue on morphologic examination In these cases, transient hyperthyroidism may result from the thyroid hormone entering the circulation during the breakdown of thyroid cancer in which hormone has been produced and stored

I shall now outline briefly the various methods of treatment of hyperthyroidism The order in which I will refer to them is not that of their relative importance Iodine plays a role in the various phases of the treatment of Graves disease, but its util-

ity has several limitations In some mild cases, the use of iodine alone, in the form of potassium iodide, Lugol's solution, or the syrup of hydriodic acid, may serve to control the hyperthyroid state for fairly long periods, but it is not an especially potent agent and, while it may lessen the symptoms, it often *fails to bring the metabolic rate down to a normal level in a* severe case A more dependable application of iodine is its use for producing a remission in preparation for thyroidectomy It has the advantage of being simple to administer It is inexpensive It is usually not toxic, although there are some who exhibit specific hypersensitivity to iodine Escape from the action of iodine represents one of the disadvantages of its *use both in the long term treatment of hyperthyroidism and in* its more intensive application preparatory for operation How iodine produces its effects is the subject of controversy According to one view, it blocks the stimulating action of the thyrotropic hormone It may do this either in the gland at the site where the thyrotropic hormone functions, as suggested by the work of Rawson, or elsewhere

The surgical treatment might be mentioned next There is little obscurity or controversy in regard to the mechanism by which surgery brings about the results There is some indication that lymphoid or muscle tissue gives rise to substances with calorigenic properties peculiar to the thyroid hormone, but, even if they do, the amounts are insufficient to produce hyperthyroidism The mechanism of action of thyroidectomy is simply the removal of the only tissue in the body with a well defined capacity to produce calorigenic substances The rapid cure by a single procedure as by the removal of a part of the thyroid is an obvious advantage There are, of course, disadvantages in surgery There is the operative risk, *but this has* become very small, because the means by which patients are prepared for surgery are effective, and these have almost eliminated the old bugaboo of the thyroid storm The possibility of myxedema after the operation is a disadvantage, although this

complication may be successfully managed The production of hypoparathyroidism with the attendant tetany is a fairly serious hazard, and although there are medical measures for treating it, this complication is certainly not a pleasant one Injury or severance of the recurrant laryngeal nerve producing paralysis of the vocal cord with resulting impairment of speech and laryngeal obstruction is also a rather serious complication, but in this the skill of the surgeon plays an important part

The first nonsurgical measure, after ordinary iodine, which achieved any conspicuous degree of popularity, was the use of the derivatives of thiourea These compounds prevent the thyroid from synthesizing its hormone They are supposed to do this by inactivating a peroxidase enzyme, the normal function of which is the oxidation of iodide to iodine Tyrosine cannot combine with the iodide ion For this elemental iodine is required, and if the thioureas prevent the production of iodine, they also prevent the synthesis of thyroid hormone

The indications for the use of thiouracil are becoming more and more clear-cut Some individuals obtain a permanent cure after varying periods of treatment with thiouracil or propyl thiouracil It would seem that all patients should receive a trial of this agent but from the practical standpoint, it is well to apply it to certain kinds of patients only, namely, those who can be relied upon to take the medicine regularly, and to adhere to a plan for regular testing of the white blood cell count and for frequent measuring of their thyroid activity In the case in which thiouracil as a permanent treatment is not feasible, it serves very well as a means to prepare the patient for thyroidectomy Given together with iodine, thiouracil provides a measure that is unsurpassed for correcting the metabolic state prior to operation

These compounds are not free of toxicity There is the rare instance of fatal agranulocytosis Death from renal failure occurs occasionally This is rare and may be prevented by proper supervision Unfortunately the close supervision that is neces

sary for this purpose requires a degree of cooperation from the patient which is not easy to secure Another practical problem arises from the fact that these compounds lead to hyperplasia of the gland and hypervascularity, providing the surgeon with a gland that is friable, hemorrhagic, sometimes ill defined, and hard to manage It is a source of real difficulty which can however, be controlled by the routine administration of iodine in the form of Lugol s solution or syrup of hydriodic acid for about 10 days to 2 weeks before the operation The iodine prevents the thyotropic hormone from stimulating the thyroid cells to hyperplasia while the thiouracil continues to suppress the synthesis of the thyroid hormone

The use of x ray to destroy the thyroid gland in the treat ment of hyperthyroidism was fairly popular at one time, but is now much less so It was chiefly applicable to patients who could not tolerate surgery, such as the poor surgical risks by reasons of heart disease, or to patients with recurrences after several surgical attempts to remove the tissue The main dis advantage of treatment with x ray is the fact that other tissues are exposed to heavy radiation in the endeavor to apply enough to the thyroid gland to suppress the formation of the hormone

X ray has been largely replaced by radioactive iodine as one of the most recent therapeutic tools It destroys thyroid tissue in much the same way as the x ray It has the advantage that adjacent tissues receive not nearly as much radiation as the thyroid itself Its administration is easy Often one dose is adequate if the calculations are properly made It is su perior to other nonsurgical management of hyperthyroidism, especially in those patients who for one reason or another fail to adhere to the regular schedule of visits and tests neces sary to avoid treatment that is either too little or too much Radioactive iodine is indicated in the rare cases of hyperthy roidism which occur in metastatic thyroid cancer, where the circumstances preclude operation and x radiation Thiouracil

and its related compounds sometimes control the hyperthyroidism in these cases, but we have evidence which indicates that the production of thyroid hormone by functional thyroid cancer differs in some respects from that of the hyperplastic gland of Graves' disease, and that the response to thiouracil is not as satisfactory as one might expect.

I should like to say a few words on the subject of how to use radioactive iodine. I hope that my spending more time discussing this therapy will not be taken to signify that it is a superior method of treatment. I do not think it is. It has serious defects at the present time. The ideal treatment has not yet been discovered. Perhaps the closest to the ideal, in the present stage of our knowledge, is subtotal thyroidectomy.

If it is decided in a particular case to treat the hyperthyroidism with radioactive iodine, the patient first receives a very small tracer or test dose of the order of 25 to 50 microcuries, the amount depending on the sensitivity of the Geiger counter which happens to be available. This step serves two very important purposes: First, it helps establish the diagnosis in some of the very obscure cases or to verify the diagnosis made in other ways; second, by means of this preliminary test it is possible to determine how much of any dose of iodine the particular thyroid gland may be expected to collect, and how long the iodine is retained. The amount of the iodine lost in the urine provides information concerning these factors. One then calculates, or what is really the case, one estimates the size of the thyroid gland which is to be treated. From these, the dosage of radioactive iodine is determined. This procedure calls for more art than science, but unfortunately too many of us are quite artless. In estimating the size of the thyroid gland, the tendency is to describe it as smaller than it is, rarely the reverse. It has been found, largely through the method of trial and error, that 150 microcuries of radioactive iodine 131 per gram of estimated thyroid

pitalization Many patients failed to show any response so that the operation would be postponed almost indefinitely During these long periods of waiting the surgeon and internist were in almost daily conference in order to spot the day which seemed optimum for the operative procedure Even so the postoperative thyroid storm was not infrequent and many of these patients died Since the use of thiouracil or propylthiouracil for preparation, I have not seen a single thyroid storm following the operation

It is no longer necessary, in most instances, to have the patient in the hospital for periods of weeks to months as used to be the case, to prepare for the surgical procedure It is now our usual practice to pursue the patient s course through visits to the clinic or the office until the signs of hyperthyroidism subside and a remission from the use of thiouracil or propylthiouracil together with iodine is established The patient is then admitted to the hospital a few days prior to the date which is set for the operation

Dr Trunnell has already referred to the need for iodine With propylthiouracil alone, the operator is confronted with a gland which is exceedingly vascular and friable and the operative procedure may be complicated by active bleeding When an adequate amount of iodine is used in the preoperative period, the gland is apt to be firm easily delivered and is not likely to present undue bleeding when the clamps are placed The view that propylthiouracil has made the surgical procedure more difficult does not coincide with my experience when iodine is also used for an adequate period and in adequate dosage

Prior to the period of this type of preoperative preparation the two stage operation was performed from time to time These were the cases in which the operation had to be abandoned after a lobectomy, and then completed about ten days later This was made necessary by the appearance of threatening signs During the operation, not infrequently the pulse

rate rose and reached very high levels This dangerous state was considered to be due to the liberation of thyroid hormone The anesthetist would often become alarmed, and it was considered wise to interrupt the operation Since the use of propylthiouracil, I have not had to do this and I believe that none of us who operates here has been forced to perform the two-stage operation

There are several other serious problems in hyperthyroidism, which have been partly or wholly solved by the new developments of the past few years A radical change has taken place in the treatment and outlook for the so-called juvenile goiter This toxic goiter always presented serious difficulties Up to as recently as 5 or 6 years ago, we were forced to operate on many children The results were almost uniformly poor Most of the juvenile group were admitted to the hospital and observed for protracted periods, sometimes months, before the operation The operative procedure was hazardous The thyroid storm was frequent The death rate was relatively high Recurrence of the hyperthyroidism following discharge from the hospital was common Since working in the Endocrine Clinic here, I have been greatly impressed with the remarkable results produced by propylthiouracil in children who take the treatment while they continue their work at school We have not operated on a single juvenile goiter

The juvenile group and the elderly persons with advanced cardiac disease made up the bulk of high risk cases They headed the list of mortalities With the new preoperative preparation, the hazards of thyroidectomy have markedly decreased Our mortality rate has become negligible, partly because high risk cases such as those I have just mentioned are less prone to come to surgery Many of them have been managed successfully with propylthiouracil, and now with radioactive iodine

Carcinoma of the thyroid may also be included among the surgical advances The diagnosis of carcinoma of the thyroid

gland has been made much more frequently in the past 10 years than previously In the past we were inclined to carry out minimal procedures in these cases It is now the practice to perform a total thyroidectomy, and many surgeons advocate radical neck dissection on the side where the tumor was removed If careful microscopic examination shows carcinoma in the other lobe, bilateral radical neck dissection should be performed Dr Trunnell has mentioned the use of radioactive iodine in conjunction with surgery

In connection with the more frequent diagnosis of carcinoma of the thyroid and the more extensive procedures in treatment, there are still some unanswered questions We frequently remove what we believe to be a nontoxic adenoma and then the pathologist reports a carcinoma We thus find ourselves in the unpleasant position of having performed only a minimal operative procedure on what was considered to be a carcinoma We have to give some thought to the question whether carcinoma of the thyroid has really become more frequent, or whether it is a case of finding more of them because we search more carefully, or whether we name more tumors carcinoma by reason of a change in pathologic criteria

Dr Shorr It is a matter of some satisfaction to find ourselves, as we do at the present time, in a position to be able to choose the type of therapy in Graves disease I have a feeling that the audience is teeming with questions Let us have them

Dr Harry Gold Dr Shorr, I have a question or two I should like to ask Only a few years ago, the new nonsurgical treatment of Graves disease was so popular a subject that the title on a program was certain to fill the seats as well as the standing room of lecture halls I attended a number of these lectures It is my recollection that quite generally speakers tolled the death knell of surgery in Graves disease The pendulum seems to have swung back from that extreme position, and the apprehension that thyroid surgeons might not find enough

in the thyroid gland to keep them busy seems to have vanished. Is that actually the case?

The answer to another question might serve as an amplification of the first Is it proper to assume that what happens to the patient with Graves disease depends on whether he lands in the hands of an expert thyroid internist or an expert thyroid surgeon? Are the two likely to offer similar advice, or is the internist apt to attempt to bring the hyperthyroidism under control with propylthiouracil and maintain the results with this drug, while the surgeon will proceed directly to utilize the propylthiouracil as a means of preparation for operation? I have encountered such differences in procedure depending on whether it was an internist or a surgeon the patient consulted I merely wonder how general that difference is

Dr Trunnell I would like to refer this question to Dr. Cohen, particularly the point with regard to the use of propylthiouracil over a long period as the definitive therapy in comparison with its use for preparation in a plan for immediate surgery

Dr Shorr Dr Cohen, would you take up this point?

Dr Eugene Cohen I should like, first, to say a word or two about the drugs During the conference, reference was frequently made to thiouracil with the implication that this compound and propylthiouracil are interchangeable This is not the case The propyl compound is much less toxic Thiouracil is responsible for several instances of fatal agranulocytosis

In regard to Dr Gold s question, I would say that about 80 per cent of the hyperthyroid patients whom I see eventually go to the surgeon I believe that Dr Shorr holds that the number who end up as surgical problems is smaller, about 60 per cent

Dr. Gold Your procedure would, I presume, be that of the internist What advice would the patient receive if he went to the surgeon first?

Dr Cohen As I stated, in my experience, after propyl thiouracil therapy, 4 out of 5 patients have in the end to be referred to the surgeon

Dr Gold That is interesting enough, but not quite an answer to my question I have not made my point clear Let us try it this way Does the surgeon advocate a trial of propyl thiouracil as a definitive form of treatment in the conventional case of Graves disease, or is his use of the drug from the very start only a measure to prepare the patient for operation?

Dr Eckel I will answer that question by saying that the surgeon should make a trial of propylthiouracil first

Dr Gold I take it, then, that you believe there are enough cases of Graves' disease in which propylthiouracil produces a lasting cure to justify the medical trial first If the trial proves unsuccessful, you turn to operation if, on the contrary it does prove successful, the surgeon continues, or should continue, the medical treatment, or possibly turn the patient over to an internist who may have more time for such things

Dr Shorr I perceive a drift toward a rigid position in the treatment of Graves disease The history of this disease should warn us that we are probably far from the end of the chapter It is too early to adopt any routine method exclusively There are always a few cases that fail to respond to one or another method There are recurrences after surgery There are failures with radioactive iodine There are also failures with propylthiouracil In view of this state continued investigation is imperative, and one cannot emphasize too strongly the need for individualizing treatment in the hope that experience with various methods might help to elucidate the etiology of Graves disease

Dr Gold How do you account for the fact that 4 out of 5 of the patients who are given a trial of propylthiouracil therapy eventually come to surgery? Is it a case of only about 20 per cent of the patients being sufficiently sensitive to the drug

the remainder either acquiring tolerance, or from the very beginning failing to respond no matter how much of the drug is given or how long the administration is continued?

Dr Cohen Almost all patients with Graves disease respond to propylthiouracil The reason we turn to surgery so often is the difficulty in maintaining the results satisfactorily over long periods of time I might mention a few of the complicating factors The thyroid gland may become enlarged and may cause pressure symptoms The degree of control of the Graves' disease by means of the drug is often inconstant, and if the heart is involved, troublesome symptoms may appear Inconstant control of the hyperthyroidism may be due to the patient s failure to take the medication regularly The drug is sometimes discontinued during infection If the patient travels, the basal metabolism and blood cholesterol tests as guides to dosage are often neglected In cases which we have observed for periods of 6 or 7 years, we have found that the required dosage varies considerably, both between patients and in the same patient at different times Some have required 200 or 300 mg of propylthiouracil daily during the entire period, while in others it was found necessary to reduce the early large doses to 75 or 50 mg daily for maintenance In these the continued use of the larger doses would lead to hypothyroidism When the drug is used for protracted periods, temporary factors appear which diminish the efficacy of the small doses giving rise to periods of Graves disease Because of these problems, and of the fact that surgical complications are so few in large medical centers we ultimately refer the major proportion of our patients for surgical operation It would be interesting to know what others have found in this connection

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Dr Gold How do you account for the fact that 4 out of 5 of the patients who are given a trial of propylthiouracil therapy eventually come to surgery? Is it a case of only about 20 per cent of the patients being sufficiently sensitive to the drug

the remainder either acquiring tolerance, or from the very beginning failing to respond no matter how much of the drug is given or how long the administration is continued?

Dr. Cohen: Almost all patients with Graves' disease respond to propylthiouracil. The reason we turn to surgery so often is the difficulty in maintaining the results satisfactorily over long periods of time. I might mention a few of the complicating factors. The thyroid gland may become enlarged and may cause pressure symptoms. The degree of control of the Graves' disease by means of the drug is often inconstant, and if the heart is involved, troublesome symptoms may appear. Inconstant control of the hyperthyroidism may be due to the patient's failure to take the medication regularly. The drug is sometimes discontinued during infection. If the patient travels, the basal metabolism and blood cholesterol tests as guides to dosage are often neglected. In cases which we have observed for periods of 6 or 7 years, we have found that the required dosage varies considerably, both between patients and in the same patient at different times. Some have required 200 or 300 mg. of propylthiouracil daily during the entire period, while in others it was found necessary to reduce the early large doses to 75 or 50 mg. daily for maintenance. In these the continued use of the larger doses would lead to hypothyroidism. When the drug is used for protracted periods, temporary factors appear which diminish the efficacy of the small doses, giving rise to periods of Graves' disease. Because of these problems, and of the fact that surgical complications are so few in large medical centers, we ultimately refer the major proportion of our patients for surgical operation. It would be interesting to know what others have found in this connection.

Dr. Gold: That has been my experience also. A satisfactory remission is easily induced by propylthiouracil, but to maintain it is another matter. Something seems to be forever happening to upset the smooth course: Unexpectedly, the basal

metabolic rate is found to have risen too high, or to fallen too low, weakness appears in association with n dema, pounding of the heart and rapid heart rate reaf in relation to the basal metabolic rate that has gone u order to avoid the need for frequent tests, I have triec plan of urging patients to keep a closer eye on symp which might serve as a guide to change in dosage befor situation is too far out of hand While this is sometimes l ful, it is not always so There are cases in which such pred pation with symptoms results in hypochondriasis Confu arises from symptoms which may bear no relation to the dition of the thyroid The patient in whom propylthiou is used as a definitive therapy in Graves' disease somet shows a striking change in attitude as the treatment is tinued At the start, the prospect of escaping an opera through the simple device of an oral medication is warml ceived, but it is not long before the operation with its outl for a stable state of health becomes a welcome suggestion relief from the unpleasant position of worry and apprehens

Dr Shorr How high is the mortality rate from the op tion in a large center such as this, and how high is it in country as a whole?

Dr Eckel I cannot say exactly, but I have no doubt the mortality following operation in large teaching cen like this one is practically nil at the present time

Dr Shorr How about the mortality rates that have b reported by other institutions, for example, the Cook Cou Hospital?

Dr Eckel They are considerably higher

Dr Shorr I wonder whether they are not sufficiently h to represent a significant risk

Dr Gold Might we have a figure which indicates the su cal mortality? Perhaps one was stated and I failed to hear

Dr Shorr Dr Eckel said that the mortality rate is virtu zero in large centers but that he is unable at the mom

to state the range between the highest and the lowest mortality rates which have been reported

I would like to call attention to one aspect of the therapy of Graves' disease which has a tendency to disappear from sight I refer to what may be termed physician weariness which makes us prone to turn to the surgeon in many cases It involves the psychodynamics of Graves' disease The patient's repeated visits afford us the opportunity to deal with it, but we fail to take full advantage of it When patients receive thiouracil therapy and return frequently for interview and examination, they provide us with an opportunity to learn something of the nature of the maladjustments which are known to be basic to the disease process, to secure better insight into the factors which initiate the process, and to assist the individual in his own reorientation as a means of avoiding recurrences

Dr Walter Modell In the case of treatment with radioactive iodine, is there any harm in the prior use of propyl thiouracil or iodine?

Dr Trunnell Yes, there is Iodine in any form, even that painted on the skin or taken as a dye for x ray of the gall bladder, may make it necessary to postpone radioactive iodine therapy for periods ranging from 3 weeks to a year

Dr Gold While we are on this subject, I would like to restate the problem of radioactive iodine therapy, and Dr Trunnell might indicate whether my understanding of it is correct The objective of its use in hyperthyroidism is to secure in the gland a quantity of radiation sufficient to destroy a proportion of overfunctioning follicles The problem of accumulating the isotope in the gland involves the experimental observation that a minute dose of iodine given to a person with hyperthyroidism will be fixed almost entirely in the thyroid, the quantitative aspects being something like this After an oral dose of less than 2 mg of iodine given to a patient with Graves disease, about 75 or 80 per cent accumulates

in the gland in a few hours How fast the gland gives up this iodine is another factor which determines the total effect of a particular dose The iodine uptake by the gland and the duration of its fixation there, as judged by urinary excretion of iodine, are two of the tests from the results of which the dose for a particular patient is estimated in order to avoid failure of therapy from too little radiation, or myxedema from too much The objection to the prior use of propylthiouracil and iodine is due then to the fact that they invalidate the results of the tests in one or another way For example, the value for excretion may be too high if there is an overabundance of iodine, for then the body reacts by greater excretion the value for uptake may be too low, if there is abundant iodine in the gland as under normal conditions, for then the gland takes up only a small part of a dose, similarly for the level of blood iodine which, if high, will result in a low uptake by the gland

Dr Trunnell That is correct

Dr Friedrich Gudernatsch After a dose of radioactive iodine, a considerable amount of the material passes into tissues other than the thyroid gland Are there any facts regarding possible damage by the radiation outside of the thyroid?

Dr Trunnell Your question is an important one We are preparing a report for the American Goiter Society on a study of the concentration of radioactive iodine in every tissue of 9 patients who died within 24 to 120 hours after a dose of the radioactive iodine When the dose of radioactive iodine is large, as in the treatment of cancer, the danger to other tissues has to be taken into consideration, but the amount given in hyperthyroidism is relatively small and presents no serious hazard to other tissues

Dr Shorr I presume that includes the pituitary also

Dr Trunnell The present method of measurement shows that the concentration in tissues is much lower than that shown by the values reported a few years ago The data sum

marized in Salter's book on the subject I think, will have to be revised downward by a large factor

Dr Gold How much total iodine is there in the "cocktail" of radioactive iodine which the patient takes?

Dr Trunnell The two are synonymous The material we use is carrier free It is all radioactive The amount of iodine is very small A measurement made before the drought showed more iodine in New York City water than in a glass of similar size containing the largest therapeutic dose we have ever given, even for cancer For radioactive iodine 131, a dose of 100 millicuries weighs only 0 08 gamma or 0 000 08 mg Since the average dose for hyperthyroidism is not to exceed 10 millicuries the weight of the iodine given in the therapeutic dose is only 0 008 gamma or 0 000 008 mg

Dr Gold Is all that taken up by the thyroid gland?

Dr Trunnell In any case which merits treatment of hyperthyroidism the amount collected by the gland should equal at least 50 per cent of the dose

Dr Shorr It sounds a little like homeopathy to me

Dr Gudernatsch I wonder if I may ask a question of a theoretic nature Since the introduction of iodine for the treatment of hyperthyroidism by Plummer of the Mayo Clinic about 30 years ago various explanations of the mode of action have been proposed Could we have a few words on the current views concerning the mode of action?

Dr Shorr Would you try that Dr Trunnell?

Dr Trunnell I might first state that the synthesis of thyroid hormone by the thyroid gland is under the influence of the thyrotrophic hormone of the anterior pituitary which is in turn controlled to some extent by the hypothalamus These facts are fairly well established but it is uncertain whether the primary control is exercised through a nervous mechanism or through another as yet unknown substance The chief ingredients of the thyroid hormone are iodine and tyrosine All the chemical steps in the elaboration of the final hormone

are not yet established As for the action of iodine in hyperthyroidism, several sites have been considered There is the view that iodine inactivates the thyrotrophic hormone Rulon W Rawson has presented strong evidence to the effect that iodine prevents the thyroid gland from responding to the thyrotrophic hormone There is still another formulation based on the observation that a rise in the level of serum iodine beyond a particular point decreases the accumulation of iodine by the thyroid gland, and the rate of hormone synthesis is depressed by a high level of iodine It is possible that all of these mechanisms may participate in the control of Graves disease by the administration of iodine It is also possible that there are other factors which have not yet been discovered

Dr Shorr I think we have run over our time We have by no means covered the whole subject and enough remains in need of discussion for another profitable session In closing I should like to say a word regarding some remarks which I made earlier and which might leave a wrong impression concerning my view on the surgical management of Graves' disease I do not wish to leave the impression that surgery in hyperthyroidism is undesirable As Dr Eckel has pointed out the surgical treatment is very effective in by far the largest number of cases It was the object of my remarks to emphasize the need for the continued study of the disease, to point out that a great deal may be learned from the application of all the various procedures, and that much may be lost by confining the management of Graves disease to any one therapeutic regimen which may at the moment seem superior, simple to apply, and which may make little demand on the physician in the long term care of the hyperthyroid patient

SUMMARY

Dr Gold The conference this afternoon leaves us with little doubt that, while we do not yet have the last word on the treatment of thyrotoxicosis, substantial advances have been made in the past few years Surgical removal of the thyroid

gland still remains the major therapeutic measure in the vast majority of patients with the conventional type of Graves' disease, but the success of the operation depends to a large degree on the quality of the preoperative preparation Up to but a few years ago, this attempt at preparation involved several weeks or even months of hospitalization, the administration of iodine, and anxious waiting for the day when a remission would be sufficiently advanced to reduce the hazard of surgical intervention Even then, failures to secure satisfactory remission were numerous and postoperative thyroid storms were frequent The use of propylthiouracil together with iodine has materially changed the outlook With these measures, adequate preoperative preparation is more rapid, more certain, and more complete It can be carried out with the patient in the ambulant state Admission to the hospital may be postponed up to a few days prior to the date set for the operation Postoperative thyroid storms have practically vanished In centers best equipped for the management of Graves' disease, mortality from thyroidectomy has virtually disappeared

Several other measures in the therapy of Graves' disease were explored in this conference the trial of propylthiouracil as a definitive form of treatment, the reasons for its failure in the majority of cases, its particular utility in juvenile goiter, the role of x ray therapy, the place of treatment with radioactive iodine and the principles involved in its application

In view of the common experience that highly effective new therapeutic measures are sometimes prone to retard the search for mechanisms in disease, a few warnings were issued namely, the danger of confining treatment to one or another simple routine, the importance of continued study of the psychodynamics of Graves disease, and the need for utilizing every opportunity provided by the prolonged care of these patients to secure insight into the basic factors involved in the process of the disorder.

Management of Myxedema

Dr Eugene F DuBois In the classical case of myxedema the diagnosis is very easy, and the treatment is relatively simple, but not all cases are classical The severity of the disease varies, and underneath the picture of myxedema there may be concealed coexisting diseases and complications of the myxedema itself It is well to remember that there are varieties of myxedema The large majority are due primarily to the failure of thyroid function, but recently attention has been called to cases of Simmond s disease, dysfunctions of the anterior lobe of the pituitary, resembling myxedema or accompanied by myxedema Attention has also been called to cases with a coexisting Addison s disease or an Addison s disease that is giving similar symptoms There are other polyglandular conditions that are associated with myxedema

We are having I think, an increasing amount of man made myxedema, made by surgeons in operations for Graves disease, when they take out a bit more thyroid than they should This condition is easily treated There are cases of myxedema from a little too much x ray therapy, and myxedema deliberately produced to relieve symptoms of coronary disease Perhaps these varieties are now less numerous than they were a few years ago Other sources of these cases are the recent drugs of the thiourea series which reduce thyroid function These drugs are useful in the treatment of hyperthyroidism They can cause transient myxedema when used in excessive amounts Radioactive iodine for the treatment of Graves disease yields a fairly high incidence of hypothyroidism and myxedema

We must not forget the complications that may be concealed in the picture of myxedema, some of which are of prime importance, such as arteriosclerosis, the myxedema heart, and coronary disease, either manifest or latent

The whole medical profession and a very considerable portion of the lay population of this country are indebted to Dr David Marine for the work he has done in the prevention and treatment of diseases of the thyroid gland We are particularly fortunate in having him here today to speak on the physiologic aspects of myxedema

Dr David Marine I appreciate the honor of participating in what Dr Shorr calls the myxedema hour' However, I have to make some reservations All of you know that new facts are hard to find and we all know that old facts are not always easy to interpret at least, we do not always interpret them alike I frankly confess to shortcomings in both categories

One can classify the case of myxedema into three general clinical groups first, infantile myxedema (sporadic and endemic cretinism) second adult myxedema, Gull s disease and third, experimental myxedema (cachexia thyreopriva) Of course, some sporadic cretins technically belong in the last category They are due to congenital absence or congenital defects of the thyroid anlage

Everyone is agreed I think, that in myxedema the major feature is loss of function of the thyroid gland, in its simplest form cachexia thyreopriva There are, however, marked differences in the response to thyroidectomy due to age, sex, and species

I shall now take up the groups in order In cretinism and Gull s disease, the thyroid undergoes a slow, progressive, specific type of atrophy which is quite distinct morphologically from the type which follows hypophysectomy I am sorry to say that at present we have no knowledge as to why the thyroid undergoes this change It has always been very difficult for me

to understand why a tissue as resistant and as viable as the thyroid should undergo atrophy from intrinsic causes alone Infections may destroy the thyroid, but infections account for only a few cases of sporadic cretinism Infection as we ordinarily understand the word will not account for this particular type of thyroid change

I have a section of a goiterous thyroid from a cretin calf in which one can still see evidence of active hyperplasia which is characteristic of the early stage and presumably is due solely to stimulation by the thyrotropic hormone In the end or fibrotic stage of the process in a human endemic cretin there are scattered shrunken thyroid follicles with markedly distorted cells—some large and hyperchromatic others highly degenerated One also may find, along with this destruction of the thyroid gland cells, mitotic figures which indicate an attempt to regenerate in spite of the destruction This we call exhaustion atrophy

The same type of change occurs in Gull s disease In such a section the thyroid lobule may be in a state of advanced atrophy but one can still recognize the lobules and the glandular elements of the follicles The lymphocytic infiltration about the follicles probably is an inflammatory reaction to the degenerating gland cells Under higher magnification one finds degenerating cells with distorted hyperchromatic nuclei sometimes along with mitotic figures just as in endemic cretinism In other words one sees a progressive destruction of the thyroid cells alongside of attempts to regenerate

In contrast with the changes which one sees in myxedema and endemic cretinism there is another type of change I have a section of the thyroid of a dog which lived about 8 months following hypophysectomy Here there is *nothing* more than an extreme degree of involution The injection of thyrotropic hormone converts these flat endothelial like cells into cuboidal or even columnar forms The *cells are just vegetating* inactive because there is nothing to stimulate them

This then is the difference between the involution of the thyroid follicle that follows withdrawal of the thyrotropic hormone (hypophysectomy) and the atrophy of the thyroid as seen in myxedema and in cretinism In the latter, involution occurs in spite of increased amounts of thyrotropic hormone, there is both anatomic and chemical evidence that the hypophysis is producing an increased amount of thyrotropic hormone, which may lead to exhaustion atrophy

Sections obtained in the early work of Lenhart and myself in Cleveland left a strong impression upon us, particularly one from a puppy, one of a litter of 4 cretin puppies with large goiters This experience emphasizes the strong regenerative stimulus present in these cases The puppy was so weak we could not do a biopsy at first so we gave the animal some iodine and took a section about five days later Despite the iodine there was considerable high follicular epithelium The thyroid follicles were widely scattered in a myxomatous stroma In another section of the same thyroid lobe 2 weeks later, the myxomatous stroma was shrinking, i e, the water was being removed and the follicles were coming closer together They looked much more like normal thyroid follicles At 6 weeks, the same lobe was practically a normal thyroid, and I might add that the animal grew to be a normal adult dog

I mentioned the similarity between the anatomic changes that one sees in endemic cretinism and myxedema (Gull s disease) There also appears to be a relationship between Graves and Gull s disease The importance of Graves' disease as a precursor of Gull s disease was emphasized in the report of the British Myxedema Commission of 1888 Virchow prior to that pointed out that almost certainly there was some fundamental connection between Graves disease and myxedema, but we all know that the pendulum has swung several times since those days Now we are back again to the view that there is some connection between these two, although superficially they appear to be opposite pathologic processes Graves' dis

ease and Gull's disease have a somewhat similar geographic distribution The highest incidence of Gull's disease occurs in those areas of the world where Graves disease is most common, that is, in those countries bordering on the Baltic and North seas and in our own country There are more cases of myxedema reported from northwestern Europe than from any other part of the world In the greater goiter districts of the world we have the other form—endemic cretinism There is about the same sex incidence in Graves disease and myxedema Perhaps myxedema is relatively more frequent in the female than is Graves disease in the latter it is something like five to one, depending upon the age and the location and in myxedema it is probably between five and ten to one In endemic cretinism it is difficult to find any figures on the sex ratio, although the four or five series that have been reported indicate that it is slightly more common in the male If there is any significance in this it is in the opposite direction of what one sees in Gull's disease

Experimentally it is extremely easy to produce cretinism (infantile myxedema) in all the commonly available mammals by thyroidectomy *alone, during their infancy, but it is very* difficult to produce myxedema in those same animals during the stage of active sexual life Also, there are species differ*ences* Herbivorous animals withstand thyroidectomy very well but carnivorous animals withstand thyroidectomy much more poorly Among adult animals there is a higher percentage of myxedema in the cat and dog than in the rabbit or sheep The same age difference, in a general way, has been noted in human cachexia strumipriva Cachexia strumipriva is much more common in the young Practically all the cases reported are between the ages of 10 and 25 years Horsley suggested that this age limitation might be related to cessation of growth

T Kocher and the Reverdin brothers noted *that not* all of the apparently total thyroidectomies resulted in cachexia

strumipriva Doubtless incomplete thyroidectomy or accessory thyroids would explain most failures but there has always been difficulty in closely correlating the amount of thyroid removed with the symptoms produced Similar observations have been made in recent years by Thompson and Thompson and others in association with subtotal thyroidectomy in the treatment of Graves disease One sees not infrequently a transient or even permanent myxedema following this operation

There is the question whether cases of Graves disease are not more susceptible to the development of myxedema and acquire this state following the removal of less thyroid gland than is necessary to cause myxedema in individuals that do not have Graves disease Such a result could be predicted because Graves disease is a natural precursor of Gull s disease The metabolic rate may be —30 with or without myxedema This all goes to show that the production of myxedema depends on more factors than merely a diminution in the amount of thyroid hormone

Cretinism occurs in the first four years of life and before much sexual development has taken place while Gull s disease occurs almost entirely during the decline of sexual life —the decline of sexual life in the female being due to one of many things (x ray radium surgery post pregnancy) Gull s disease in the male also occurs during the decline of sexual life

It looks as if some glandular interrelations may be involved in promoting or inhibiting the onset of myxedema such as the thyroid gonad the thyroid hypophysis-gonad and the thyroid adrenal I won t go into these because my time is nearly up

I might just mention a few experiences which indicate these glandular interrelations in myxedema We studied the urinary excretion of androgens in 3 cases of Gull s disease We used the capon comb growth promoting test We examined

a 72-hour specimen of urine, although in such a work a 30-day specimen is preferable. I do not want to make too much of this test, but if carefully done I think it is superior to the colorimetric methods now available. In a female, age 50, a diagnosis of Gull's disease was made by several competent internists. The basal metabolic rate was −23 and the total androgen excretion during the 3-day period, in 6,800 cc. of urine, was 0.86 mg., calculated as androsterone. Desiccated thyroid was then given, and in the course of 10 days the dose was brought up to a grain daily. After 93 days another 3-day specimen of urine (6,690 cc.) showed a marked increase in androgen excretion. It rose to 4 mg. and the basal metabolic rate rose to +14. Fifty-six days later a third specimen of urine (5,570 cc.) showed an androgen output of 3.5 mg.

Another patient, a male, aged 54, was observed at Mt. Sinai Hospital through the courtesy of Dr. B. S. Oppenheimer. The total excretion of androgens determined in a similar manner was 1.1 mg. before treatment, which is definitely below normal. After 47 days of treatment with desiccated thyroid (½ grain daily), there was a significant rise in androgen excretion to 3.26 mg. and the basal metabolic rate rose from −22 to −4. Three cases are not enough from which to draw conclusions and more cases must be studied to see if this rise in androgen excretion occurs regularly. Dr. Rosen was unable to demonstrate any change in the estrogen excretion.

Where do the androgens come from in postmenopausal women? They could come from the adrenal cortex. We know that the functions of the thyroid and adrenal cortex are interrelated. There are numerous cases in the literature indicating that the feeding of thyroid increases androgen production and excretion. A recent case reported by McCullagh from the Cleveland Clinic is strongly suggestive. A male, age 50, came to the clinic complaining of sexual impotency. After treatment with testosterone propionate, he promptly regained sexual potency, but his metabolic rate remained −32. Desiccated

thyroid was then substituted for the testosterone The result was that his metabolic rate returned to normal and the sexual potency was maintained Androgen excretion studies were not made in this case

In closing, I might state that we are nowhere near a solution of the myxedema problem in spite of the fact that, as Dr Shorr will tell you, we have nearly a 100 per cent satisfactory therapy in Gull s disease In my opinion, a complete solution of the problem of myxedema cannot be expected until we have much more exact knowledge of the various endocrine interrelations than we now possess

Dr DuBois Dr Shorr will speak on the general medical treatment

Dr Ephraim Shorr The broad background of the pathophysiology of myxedema, that Dr Marine has given us, permits me to simplify my discussion His remarks also demonstrate how the possession of a successful therapeutic agent tends to oversimplify our concept of a clinical syndrome It is becoming obvious that a condition such as myxedema cannot be assigned to the thyroid apparatus alone Before passing to the treatment of myxedema it might be worthwhile to pause at the problems presented by the diagnosis As a clinical syndrome its manifestations are generally so clear cut that one might anticipate no difficulty in recognizing it For that reason it is disquieting to see how long a period generally elapses between the development of symptoms and the recognition of their significance by the practitioner I have before me the charts of 9 cases which have been followed in the Out Patient Department The duration of symptoms prior to recognition was as follows 15 years 10 years 7 years, 6 years, 5 years 4 years, 3 years, 1 year, and 3 months This is altogether too long and points to some sources of confusion which contribute to this lag

Analyses of these cases have brought out some of the more common causes for this delay Cardiac symptoms have often

predominated and have led the physician to regard the phenomena to be on a purely cardiovascular basis The pallor common to this condition has frequently led to a diagnosis of anemia, too often uncorroborated by laboratory tests, and to its treatment on this basis The edema and anemia have in other cases prompted the diagnosis of Bright's disease These appear to comprise the most common incorrect diagnoses I do not mean to imply that all cases of myxedema are classical in their symptomatology and laboratory findings Difficulties in establishing a diagnosis are occasionally encountered but well recognized and reliable methods are available, which in combination provide extremely reliable diagnostic criteria

On the clinical side, there is generalized edema, changes in the skin and hair, sensitivity to cold, impairment of mental alertness, gain of weight, bradycardia, and lowering of the voice. On the laboratory side, the lowered basal metabolic rate and the elevated blood cholesterol values are most commonly employed as criteria Circulatory studies yield valuable information in the form of changes in the size of the heart and in the electrocardiogram, the slower circulation time, and diminished minute volume We have recently called attention to the value of studies of creatin metabolism in adult myxedema The untreated case of myxedema will present entirely normal values for spontaneous creatin and creatin tolerance Following the administration of thyroid, a temporary creatinuria and impairment of creatin tolerance occurs thus, the development of these abnormal creatin values after small doses of thyroid, as little as 30 mg daily of desiccated thyroid, is proving an unusually sensitive indicator of the existence of myxedema In children where the picture is frequently atypical, the determination of the bone age is of great help The determination of serum organic iodine is proving a valuable index of myxedema and, although at the moment more of academic than of practical interest, the level of circulating thyroid hormone is generally elevated

Once the diagnosis is made, various problems present themselves: the choice of therapeutic agent, the mode of administration, and the therapeutic goal. These may be best discussed by an example of a specific case.

The case I have chosen is that of myxedema in a woman of 26. Her marriage at 18 was followed by 4 pregnancies in rapid succession, each pregnancy resulting in more and more evidence of myxedema until it finally became permanent. On admission, her physical appearance was typical of myxedema. The thyroid was palpable and slightly enlarged. Her basal metabolic rate lay between —30 and —35. Her blood cholesterol was 430 mg. per cent. Her nitrogen output in the urine was low, reflecting the lowered protein metabolism of this condition. Her circulation time was 14.6 seconds and her cardiac output, 1.26 liters per square meter per minute. The surface area of the heart was 160 square centimeters. The electrocardiogram showed low voltage QRS, low T-wave, and a P-R interval of 0.54 second. Her weight was 80 kilograms.

In most cases of myxedema the thyroid histology is virtually that of total atrophy so that significant restoration of function cannot be anticipated from the administration of iodine. Replacement therapy with thyroid hormone must be employed. In this case, because of the thyroid enlargement, iodine was tried for a period of 20 days to ascertain whether there was sufficient residual thyroid tissue which might undergo involution and elaborate enough thyroid hormone to abolish the myxedema. The iodine was ineffectual so that replacement therapy was obviously necessary.

Of the available thyroid preparations, standardized desiccated thyroid is generally agreed upon as the preparation of choice. The action of thyroxin by mouth is unreliable, and there are very few indications for its intravenous use. Indeed, except under unusual circumstances thyroxin has no place in the general therapy of myxedema. The advantages of standardized desiccated thyroid lie in its uniform action by mouth,

its low cost, the ease of administration, and the fact that it permits the gradual restoration of function by graded doses Once the proper maintenance level is ascertained a well standardized thyroid preparation can be depended on to maintain the results over years It is wise to choose one or another preparation of standardized desiccated thyroid and by using it exclusively, to learn what may be expected from it

The second problem is that of dosage, and the speed with which normal metabolic functions are to be restored It is generally agreed that the initial dose of desiccated thyroid should be small, that the dose should be raised slowly and that complete replacement should not be achieved in less than two months The reasons for this long and cautious regimen will become apparent when we follow the effects of thyroid administration in the case of this young woman The initial dose which she received was 15 mg of desiccated thyroid daily The dose was increased at first by 15 mg and then by 30 mg steps until full replacement was achieved as indicated by abolition of the signs and symptoms and by restoration to normal of the values of the various criteria The dose was raised when laboratory and clinical signs indicated that maximal effects had not been achieved by the preceding dose level The choice of the low initial dose was based on the well known biological phenomenon that the effects of hormones are in direct proportion to the degree of insufficiency so that the influence of 15 mg in complete myxedema may be as great as 60 mg after thyroid insufficiency has been partially corrected

The administration of desiccated thyroid brought about a series of characteristic changes both in the symptoms and appearance of the patient and in the laboratory findings The basal metabolic rate gradually rose to a level of —3 on a dose of 180 mg of desiccated thyroid per day The cholesterol level in the blood fell from 430 mg to the normal value of 200 mg per cent The urinary nitrogen rose to normal values A crea

tinuria developed, reaching a level of 800 mg. of spontaneous creatin, and then gradually fell. With this there was a temporary impairment of creatin tolerance. The circulation time fell from 14.6 to 9.9 seconds. The cardiac output rose from 1.26 to 2.05 liters per square meter per minute, and the cardiac area shrank from 160 square centimeters to 115. The electrocardiogram showed an increase in amplitude of the QRS complexes and the T-waves, and a diminution of the P-R interval to 0.24 second. All of these latter changes reflect a great increase in the amount of cardiac work. They indicate the reasons for the prolonged therapeutic course and the cautious dosage. The increased demands placed on the cardiovascular system by a 50 per cent increase in metabolic requirements resulting from the elevated basal metabolism is a strain of considerable magnitude. Most cases of myxedema fall into the postmenopausal age group where degenerative vascular changes contribute to the difficulty of meeting this increased demand. It is no wonder then that we so frequently encounter instances where cardiovascular damage results from too rapid restoration to normal metabolic levels. Therein lies the real danger of one of those older regimens which called for the intravenous administration of a full replacement dose of thyroxin.

One of my earliest experiences with myxedema brought this lesson to me very strikingly. I treated an ambulatory case of myxedema in the Out-Patient Department, with a dose of desiccated thyroid of 30 mg. daily for one week, and 45 mg. daily for the second week. At the end of the second week, I was notified that my patient had been admitted to the hospital with cardiac decompensation. Her newly acquired well-being under thyroid administration had led to greater physical activity and a sudden strain to which her cardiovascular system was as yet unable to adapt itself. Indeed, even in cases falling into the older age group which are carefully watched in the hospital and are treated cautiously, anginal attacks, mild seizures

of congestive failure, and even coronary occlusion are occasionally encountered

These observations have a bearing on the goal of replacement therapy While in the case of many patients, full replacement can be successfully achieved, with restoration of the various criteria to normal levels, there are others for whom a normal basal metabolic rate and complete replacement are undesirable This group comprises those with low cardiac reserve Nature has done a complete thyroidectomy, a measure that has been deliberately employed in recent years for diminishing cardiac work in patients with heart disease We can take advantage of this opportunity and choose that thyroid dosage which achieves relief of the uncomfortable symptoms of myxedema and at the same time does not increase too greatly the work demanded of the cardiovascular system

Means recently called attention to one other possible complication which may arise in myxedema during thyroid therapy This consisted of a temporary adrenal insufficiency which had to be combated by administration of large amounts of sodium chloride Up to now we have not met with this complication in the patients treated in this clinic

As a rule, the amount of desiccated thyroid necessary for complete replacement in myxedema is relatively small I have sampled at random a few of the charts of patients who are being maintained at complete replacement levels, to illustrate the usual range of dosage These are the figures for the amount of *desiccated thyroid taken daily 180 mg, 150 mg, 120 mg* 120 mg, 120 mg, 90 mg, 90 mg, 75 mg, 60 mg, 60 mg, 60 mg There is a rule to which, to be sure, there must be an occasional exception—that whenever 180 mg of desiccated *thyroid given* daily fail to relieve the signs and symptoms in a patient with supposed myxedema, some other etiology must be suspected

As regards postoperative myxedema and cretinism the same diagnostic criteria and therapeutic regimen should be em

ployed as with Gull's disease. In the case of the cretins, early diagnosis and treatment favor a restoration to normal well-being, but many residual defects may be anticipated.

Dr. DuBois: Dr. Shorr, the doses mentioned refer to U.S.P. desiccated thyroid, do they not?

Dr. Shorr: For the past twenty years we have used in this clinic one brand of a thyroid preparation, and we have found it very uniform. It contains 0.2 per cent of iodine. In patients who have been carefully followed for four or five years, it is quite amazing to see how constant its action is. I believe that everyone should work with one preparation to assure himself of its potency and get to know how to use it.

Dr. DuBois: That is the lesson we learned in discussing digitalis. I think there has been a good deal of confusion in the literature of myxedema on account of the fact that some preparations of thyroid are very much weaker than the U.S.P. standard.

Dr. Harry Gold: Would Dr. Shorr state why we don't use thyroxin more frequently, since it is a pure chemical?

Dr. Shorr: Its action by mouth is much less regular, due to irregular absorption, in contrast to the regular effects obtained from the oral administration of desiccated thyroid. The necessity for intravenous medication with thyroxin is extremely rare.

Dr. McKeen Cattell. Are the doses you employ sufficient to cover the theoretic total needs for thyroid hormone in completely deficient patients?

Dr. Shorr: They are. The doses that I stated will correct all the physiologic defects and bring about complete symptomatic relief. As, I think, Dr. Marine pointed out, one may see a few acini here and there which differ from those in normal glands in the absence of colloid, but this indicates that any contribution by the gland must be slight. Would that be your feeling, Dr. Marine?

Dr. Marine: I would say that most myxedemas have some



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of congestive failure, and even coronary occlusion are occasionally encountered

These observations have a bearing on the goal of replacement therapy While in the case of many patients, full replacement can be successfully achieved, with restoration of the various criteria to normal levels, there are others for whom a normal basal metabolic rate and complete replacement are undesirable This group comprises those with low cardiac reserve Nature has done a complete thyroidectomy, a measure that has been deliberately employed in recent years for diminishing cardiac work in patients with heart disease We can take advantage of this opportunity and choose that thyroid dosage which achieves relief of the uncomfortable symptoms of myxedema and at the same time does not increase too greatly the work demanded of the cardiovascular system

Means recently called attention to one other possible complication which may arise in myxedema during thyroid therapy This consisted of a temporary adrenal insufficiency which had to be combated by administration of large amounts of sodium chloride Up to now we have not met with this complication in the patients treated in this clinic

As a rule, the amount of desiccated thyroid necessary for complete replacement in myxedema is relatively small I have sampled at random a few of the charts of patients who are being maintained at complete replacement levels, to illustrate the usual range of dosage These are the figures for the amount of desiccated thyroid taken daily 180 mg, 150 mg, 120 mg 120 mg, 120 mg, 90 mg, 90 mg, 75 mg, 60 mg 60 mg, 60 mg *There is a rule to which, to be sure, there must be an occasional* exception—that whenever 180 mg of desiccated thyroid given daily fail to relieve the signs and symptoms in a patient with supposed myxedema, some other etiology must be suspected

As regards postoperative myxedema and cretinism, the same diagnostic criteria and therapeutic regimen should be em

matic change Replacement therapy was instituted with considerable relief of symptoms After about six months of such treatment, she ceased taking thyroid and has since been very well without replacement therapy I think that fits in with Dr Marine's conception of the picture of thyroid insufficiency with adequate metabolic rate but inadequate thyroid hormone formation for other functions

Dr DuBois I would like to add a word of caution in the diagnosis of myxedema with normal metabolic rate Of course, there is no one laboratory test that is diagnostic in all cases

I might add a few words about the use of the basal metabolism in diagnosis and treatment You must remember that a good many persons with metabolisms of −15 are within the normal range, and a few as low even as −20 are within the normal range Statistically, however, the chances are that they are abnormal You will see reports in the literature of large groups of cases with low metabolism, averaging around −20, that are labeled mild myxedema Relatively few of these cases are reported from the clinics where they are making special studies of thyroid disease relatively few from such places as Dr Means clinic in the Massachusetts General Hospital or in the Mayo Clinic A good many are reported by doctors who are enthusiastic over the results they obtain from thyroid medication I think there are patients with myxedema in that range, and those usually have some of the classical symptoms of myxedema which improve distinctly and satisfactorily with thyroid medication However, there are a good many who are accused of having myxedema at that level but who do not have it. These are patients below par They show fatigue They are perhaps anemic They tire easily They have menstrual disturbances or sterility Many of them improve with thyroid medication Whether or not they have a real thyroid deficiency we are not quite sure, but undoubtedly the practitioner is labeling as myxedema a great many patients who have never had it

thyroid function, but it is negligible when they reach the state where the metabolic rate goes down to −30

Dr Shorr Should there be any uncertainty, I think it good practice to put such a patient on a course of iodine If the symptoms and the physiologic abnormalities are not corrected, then it is certain that any residual function is negligible

Dr Marine I might add that Kocher has one of the best accounts of cretinism in America He had a considerable number of patients treated with syrup of hydriodic acid alone This remedy gave some relief of the symptoms and in several an increase in growth One would have to infer from this that there was some thyroid present in clinical myxedema In experimental animals we cannot get any effect from giving iodine if the animal has no thyroid tissue

Dr DuBois I might say that syrup of hydriodic acid is our favorite preparation of iodine on account of its relatively pleasant taste

Dr Gold Do we recognize any hypothyroidism or myxedema with a normal basal metabolic rate? From time to time one encounters patients who have the clinical signs and symptoms of myxedema but turn out to have a normal metabolic rate

Dr Marine That is a very difficult question I think that the metabolic rate does not depend on the thyroid alone You can have a high rate after removal of much of the thyroid and there may be some thyroid insufficiency in relation to its influences on the function of other organs not connected with the metabolic rate We are getting into a theoretic problem We ought to leave it at this point

Dr Gold Is there any experience among the group here in the treatment of these cases?

Dr Shorr Yes, I remember one such case A woman in her thirties with a basal metabolic rate of about −5, had definite evidence of myxedema, and on iodine showed no sympto-

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Student: Does the dosage of thyroid vary with the activ of the individual? Would you use more thyroid material d ing periods of greatly increased exercise?

Dr. DuBois: Would it be like insulin in that respect?

Dr. Shorr: I do not think we have any methods sensiti enough to detect the small differences that might exist.

Dr. Janet Travell: Are there any other dangers connect with the use of thyroid in myxedema besides those which I Shorr mentioned, that is, danger of precipitating myocard failure or the anginal syndrome?

Dr. Shorr: I might refer to Means' report of 2 patients wl on thyroid replacement therapy, developed signs of acı adrenal insufficiency and had to be treated with large amour of salt.

Dr. DuBois: There is one more detail that Means brin out, the danger of morphine in myxedema. What should the dosage of morphine in myxedema—none at all, or can y use it if it becomes necessary?

Dr. Shorr: I would suggest none at all, if possible.

Student: Is the arteriosclerosis in typical hypothyroidism dı to the thyroid disorder or can it be explained by the age the group?

Dr. Shorr: The situation is too complex for us to be certa of the significance of arteriosclerotic changes. Long-standir myxedema occurring in the third decade, as in the patient discussed, may be entirely free of arteriosclerotic changes.

Dr. Travell: If untoward results do not develop early i the course of treatment, are they apt to develop subsequently

Dr. Shorr: Yes. Cardiac symptoms may result from too su den assumption of more work quite apart from the existen of cardiovascular disease. There is, in addition, the patient i whom a greater load is imposed on a heart with coronary di ease, and this results in anginal symptoms.

Dr. Walter Modell: I wonder whether there is an explana tion for the tremendous resistance to the thyroid hormon

which is exhibited by the patient with nephrosis to whom very large amounts of thyroxin have been administered intravenously without producing any appreciable effect.

Dr. Shorr: There are undoubtedly great differences in sensitivity to thyroid exhibited by many normal individuals. We don't know the reason for the sensitivity of the patient with myxedema, and for the insensitivity of the normal individual and the patient with nephrosis.

Dr. DuBois: I should like to say that the striking point brought out in regard to therapeusis is the need of great caution in treatment, that is, beginning it very gradually and watching the patient with extreme care. In planning the treatment we should bear in mind the underlying pathologic physiology of the condition. Here are people, usually women, who have been going around for months or perhaps years with a lowered metabolism, not only a lowered basal metabolism, although it is on the average 30 to 40 per cent below the standard, but also a lowered total metabolism. They are not as active as most people. They try to keep quiet. As a result, the total metabolism has been lowered, and there has been a diminished demand on all the functions of the body. The organs of the body have more or less adapted themselves to these lethargic conditions of the patient. When thyroxin was first discovered, there was the temptation to use it dramatically in the treatment of myxedema, and some patients received even the full therapeutic dose intravenously. The results were dramatic. The patient became quite seriously ill. There were general discomforts: severe pain, nausea, fever, and sometimes mental symptoms. The metabolism returned to normal after this dose, and the patients eventually got along all right, but they did it in the hard way, the uncomfortable way.

Why is there danger in such a practice? Suppose a woman has a metabolism of —40, and you raise it suddenly to normal. That sounds fine. However, a metabolism of —40 means 60

per cent of the normal You don't raise it 40 per cent when it goes up to 100, you raise it 66 per cent That would be comparable to taking a normal person with a metabolism of 100 and raising it to plus 66 That imposes a great strain on the organism, particularly when we realize that that increase goes on night and day

There is no particular need for hurry in the treatment of hypothyroidism The patient has had the condition for a long time *When you start treatment,* you are really initiating a convalescence, and you have to use the technic of convalescence, convalescence from a long illness I don t know if you all realize that the management of convalescence is much more difficult than the management of an acute illness It requires much more acumen on the part of the clinician

Student Does the dose of thyroid depend on the level of the basal metabolic rate at the time treatment is started?

Dr DuBois Dr Shorr has already indicated that the lower the metabolic rate the greater is the effect of a given dose of thyroid in a patient with myxedema Means has worked out some nice averages A dose of ½ grain a day will bring the patient's metabolism up to about —20, and will hold it there An additional dose of ½ grain, making it 1 grain a day, will hold it at about —10 Adding another ½ grain to make the dose 1½ grains, will bring it up to about —5 Then a jump from that to 3 grains holds the metabolic rate at about normal So you see, you get about half of the full effect from the first ½ grain I hope to hear something about that from the pharmacologists *if they will discuss that point* In increasing the dose, remember that there is a long lag in the effects of the new level of dosage, several weeks some say months, before you attain the full therapeutic effect of the new dosage level If you step it up too fast, you will be getting the picture that reflects the dosage of the previous month By taking your time in this, in the course of two or three months, or perhaps a

month or so longer, you can work up to about the maintenance level for that individual patient.

There is further a good deal of individual variation in dosage. In the first place you don't know what that patient's basal metabolism was when normal, or what it would be if the patient were normal. It might be anywhere between +10 per cent and −10 or 15 per cent, and you cannot use an arbitrary rule of bringing the metabolism up to exactly on the dot of the average normal. You have to adjust it by the symptoms of the patient, and you have to watch them, carefully steering between overdosage and underdosage. You have to make the changes slowly.

Student: How constant are different preparations of thyroid?

Dr. DuBois: They vary considerably. The U.S P. preparations are fairly uniform, but the Parke Davis is stronger and the Burroughs Wellcome preparations much weaker. I hope Dr. Gold will go into these relative strengths. You have to check up on the particular kind of thyroid, of dried thyroid substance, that the patients are using I remember one patient of mine who had been getting along very well on a Burroughs Wellcome preparation, I have forgotten the exact dosage, but it had been standardized She was doing well when gradually the symptoms of myxedema began to reappear, and before long she was rather badly off. I questioned her regarding the medication She had been taking the specified number of Burroughs Wellcome tablets regularly. She was a very conscientious person I asked her to bring me the bottle, and looked at it, and there in small print on the label it said, "Thyroid 1/100 grain." The druggist had given her a 1/100 grain tablet instead of a 1 grain tablet. Why any firm would make a preparation as weak as that, I don't know, but it is something to look out for.

Dr. Gold: Do you see any thin, scrawny myxedemas? Does finding the patient pretty thin, usually rule out myxedema?

Dr Shorr No One of the most classic cases in our nutrition department at the hospital was a very thin young woman She was driving herself all the time, and she wondered why with such an adequate intake of food and good general habits she should have to push herself She was a classic myxedema by all of the laboratory indices We used basal rate, cholesterol and circulatory phenomena, which Dr Evans was good enough to study while he was here with Dr Stewart She also showed a perfectly classical response to replacement therapy

Dr Gold Did she get fat?

Dr Shorr She did not get fat She has since gained a little weight I saw her recently, about four years after the discovery of her myxedema and she has gained possibly 10 lbs She was a striking example of the thin myxedematous patient

Dr DuBois The classical case of myxedema is said to have a gain in weight Dr William Plummer, of the Mayo Clinic has made a careful analysis of the weights of his patients 200 of them, and has found that the majority do show weights that are above the average, above the normal expectancy for height About two thirds of them have an increase in weight but the average amount of edema in his patients is 13 lbs If a patient has gained only 13 lbs in weight it does not mean anything added to the fat or muscles of the body Thirty eight per cent of his patients showed weights that were below the normal expectancy, and that means that they were below 13 lbs , plus a loss in body tissue By that I mean that, if they were just at the normal weight, 13 lbs of edema were taking the place of 13 lbs of good normal tissue In general, the severer cases were the ones that showed the loss in weight and that points to an undernutrition of the whole body

Student I would like to ask Dr DuBois about the management of one of those patients with a —10 B M R who does not have an obvious myxedema Is there any indication for giving thyroid to such a person? This is a person with fatigue and no obvious signs other than that

Dr DuBois A great many papers in the literature report excellent results, without much of a scientific background There is a question as to what the thyroid medication is really doing By just going to the doctor they are paying more attention to their diet, and they are being encouraged Someone is taking an interest in their case Their lives are better regulated They are cheered up There are a great many factors besides the thyroid that go into that prescription

Doctor Is it conceivable that they might have a myxedema that is of lesser degree?

Dr DuBois Yes, it is perfectly conceivable that their normal metabolism would be, say, —10, and they are running along 20 per cent lower than they should be I think there are relatively few of those cases and that the more careful the clinic, the fewer you will find who are labeled myxedema I don't see there is any harm, however, in trying thyroid medication for a short time

Dr C H Wheeler How about the case of the obese female who is trying to reduce her weight and is found to have a basal metabolism of —12 or 15, and who is given thyroid as an adjuvant to the dietary treatment? Is that to be recommended, do you think?

Dr DuBois I think, if it is done very cautiously and carefully, thyroid is of use in obesity It has to be watched. I don't think it should be a routine treatment

Visitor I would like to ask about the use of thyroid treatment in private practice where basal metabolism studies are not easily obtained I refer to practice among poorer people, that is not associated with clinics or large hospitals Is it feasible to carry people along with thyroid medication using only clinical guides after, let us say, an initial metabolism test?

Dr DuBois It can be done by carefully watching the patient, using good clinical judgment After all, you have to do that even if you do use basal metabolism tests The final

criterion is the condition of the patient and the judgment of the doctor It can be done, and you have to do it

Dr Shorr Specificity of response is a very good indication of genuine myxedema because these patients respond very quickly, and in two or three weeks they are aware of a decided improvement in well being In borderline cases, however, and they are not uncommon, people who feel sluggish, who are tired and slow down toward the end of the day, and who frequently get a pickup in the afternoon if they have taken thyroid, I find myself unable to believe that the moderate improvement is very significant The diagnosis in these cases is uncertain without laboratory data Every patient with genuine myxedema develops a significant creatinuria after the administration of even a grain of thyroid a day There is always a fall in the cholesterol With the cessation of treatment with thyroid in the true myxedematous patient there results a sharp rebound A great many workers feel that the rebound in cholesterol after cessation is even more significant than the change which occurs on administration of thyroid The experience that we all have with people who feel better on thyroid, who get used to taking thyroid, who feel let down after stopping thyroid, but who fail in every test to reveal thyroid insufficiency, shows the difficulty of solely subjective observations Very often, as Dr DuBois pointed out, ordinary hygienic measures, possibly some tea at 4 30, a sandwich and a cooky will take that tired feeling away in a person who has resorted to thyroid for a long time

Dr Gold How about a working rule for a course of treatment with thyroid material in the case of suspected hypothyroidism? You have a patient who, let us say, has symptoms suggesting myxedema and either you cannot do a basal metabolism test or you find it near the border, —12 You decide to try thyroid Would it do to proceed in this way Give doses up to 3 grains a day, and if at the end of a week or two, no distinct signs of improvement appear, one may then assume that

it either is not a case of myxedema or that thyroid is not going to help? Would you agree to that as a working rule?

Dr. Shorr: I think you can be reasonably sure of that. Our cases here with complete myxedema have required on an average 2 grains a day, and of the 20 or 30 cases that we have had under treatment, none has required more than 3 grains.

Dr. DuBois: Would not 3 grains be a pretty large dose? I should think it would be a better procedure to give 1 or 2 grains, and keep it up a month before you make your evaluation.

Dr. Gold: A month with a daily grain or two, and then, if no response, you are fairly sure it is not myxedema?

Dr. Shorr: I think so.

Dr. DuBois: Have you any figures on the strength of different preparations?

Dr. Gold: The U.S P. preparations of thyroid are all assayed for their iodine content, and they are supposed to have a potency of approximately 2 mg of iodine per gram of thyroid. Many people refer to it as extract of thyroid It is not an extract. It is just the gland deprived of connective tissue and fat, dried, and powdered In the older pharmacopoeias it used to be called "dried thyroid." The newer revisions of the *Pharmacopoeia* do not label it "dried thyroid" but just "thyroid."

There have been some analyses of market preparations of thyroid. Preparations from different sources do not always produce equal effects in terms of their iodine content. Thompson (*J.A M.A.*, 1935) and his co workers reported certain lots of beef and sheep thyroid produced less effect than hog thyroid in doses containing similar amounts of iodine Lerman and Salter analyzed 6 preparations and found the iodine content to vary all the way from about 2 mg to 4 mg per gram of the dried gland They examined those preparations further for the amount of thyroxin iodine, and found that this varied from 16 to 42 per cent. Examination of these specimens, however,

in relation to their calorigenic action showed they were not very far apart, which means that there are some factors relating to the potency of thyroid materials not directly explained by either the iodine or thyroxin content

It is, perhaps, well to use thyroid material made by the same manufacturer, rather than to shift from one to another because in spite of the standardization by the iodine method there are differences in different thyroid materials which cannot be tested for at the present time This will eliminate at least one source of variation

There is just one other material which is used besides the thyroid itself, and that is thyroxin I might call your attention to the fact that the *Pharmacopoeia* states the dose of thyroid as 60 mg and of thyroxin as 0 5 mg These are supposed to be equivalent The dose of thyroid represents only 0 12 mg of iodine, while of thyroxin 0 32 mg of iodine This indicates that thyroxin iodine is not as effective in therapy as the iodine present in the original gland This may in part be due to the fact that it is not as well absorbed from the gastrointestinal tract, which would be in line with what Dr Shorr has said about thyroxin being irregular in its action and not as dependable as thyroid

SUMMARY

Dr Gold The diagnosis of myxedema sometimes presents difficulties It is to be distinguished from anterior pituitary disorders (Simmond s disease) and Addison s disease It is sometimes confused with primary heart disease anemia and Bright s disease It may exist as a complication or an accompaniment of other diseases There are substandard states of health associated with weakness and fatigue which are frequently treated as cases of myxedema because they present a slightly lower than the usual normal basal metabolic rate There is considerable doubt as to whether thyroid medication produces any specific benefits in these cases and whether the

reported benefits may not be the result of other therapeutic measures usually employed at the same time.

Dr. Marine presented a very provocative discussion of the pathologic physiology of myxedema. He pointed out the difference between the thyroid gland after the removal of the pituitary and the thyroid gland in Gull's disease. In the former the thyroid gland shows atrophy without signs of attempts at regeneration; in the latter atrophy and regenerative hyperplasia may exist side by side. The thyrotropic hormone of the pituitary is active in Gull's disease and continues to stimulate the thyroid gland to activity, a fact which may lead to exhaustion atrophy. He indicated the glandular interrelations in myxedema by the example of the marked increase in urinary androgens during the administration of thyroid in patients with myxedema.

While most cases of myxedema have low basal metabolic rates, there are many cases with very low basal metabolic rates who do not show signs of myxedema. There are some cases of myxedema with normal values for the basal metabolism. Most cases of myxedema are overweight; some are underweight. This indicates the complexity of the problem of thyroid deficiency.

In the therapy of myxedema, the object is primarily to restore the patient to a metabolic state most consistent with optimum health. Reversal of laboratory tests to normal, such as the basal metabolic rate and the blood cholesterol, usually accompany such restoration. There is some danger, however, in depending upon these alone since hypothyroidism may serve as a protective mechanism in cases of advanced circulatory disease. Restoration of the metabolism to the average normal sometimes results in attacks of angina pectoris and overloading of the circulation with resulting failure. The patient's symptoms serve as a guide to the extent to which reversal of the myxedema state is to be carried. The therapy should be developed very slowly, over a period of a few months,

in order to enable the patient to make appropriate adjustments to the increase in metabolism

The myxedema patient is very sensitive to thyroid medication and, if a dose as large as 180 mg daily fails to produce significant improvement, there is reason for doubting the accuracy of the diagnosis

While there are patients with Gull s disease in whom the residual active thyroid may be stimulated by iodine dried thyroid is the most important medication The method of its administration was discussed The dried thyroid is preferable to the pure hormone thyroxin because it is apparently better absorbed and its action is therefore, more regular and dependable It is well to confine one s practice to the use of one preparation of thyroid because in spite of the standardization of U S P thyroid preparations there are differences in the effects produced by thyroid preparations from different sources even when in terms of iodine, the doses that are given appear to be equivalent.

Treatment of Cardiovascular Manifestations of Thyroid Disorders

Dr McKeen Cattell Not infrequently the hour has proved too short to cover completely the topic assigned and that was the case with the two conferences on the diseases of the thyroid We thought it would be worthwhile this afternoon to discuss further a special aspect of this problem, that is, the treatment of the cardiovascular complications of thyroid disease Dr Gold, will you open the discussion?

Dr Harry Gold Let me state at the outset that one should distinguish between cardiovascular complications and cardiovascular manifestations of thyroid disease

A patient with Graves disease may be subject to rheumatic heart disease, arteriosclerotic disease, or some other form of heart disease, and in that case we have one disease complicating the problems of the other I think it is intended to relate the discussion today not to that group, but rather to those disorders of the heart which occur as the direct result of the thyroid disturbance The designation, cardiovascular complications of thyroid disease is not strictly accurate as applied to this group The cases in this group should be referred to as the cardiovascular manifestations of thyroid disease Cardiac disturbances may be the dominant manifestations of thyroid disease in some cases

These disorders are quite common The heart is often involved in thyroid disease Rapid heart action occurs in the vast majority—not in all, but in most of the cases The cardiac

difficulties present *pressing problems, I should say,* in about one quarter of all the cases perhaps even more In many cases the heart presents the most serious aspects of Graves disease In a small number of patients—I am not sure how large that number is—the cardiac disturbances are the only manifestations, at least for a period—sometimes a period of years—after which the true nature of the cardiac disturbance reveals itself as one which has its basis in so-called masked hyperthyroidism "

The more common disorders are sinus tachycardia ectopic auricular tachycardia, auricular fibrillation, and congestive failure Some patients have more than one type of abnormal rhythm Auricular flutter is a less common accompaniment Auriculoventricular block is also uncommon

The chief agents which are effective in the control of these disorders are quinidine, digitalis, Mecholyl, and iodine We may add thiouracil Thyroidectomy cures in the vast majority of cases of Graves disease The administration of thyroid materials is helpful in the occasional case in which the underlying cause is hypothyroidism or myxedema

There are certain special features of the cardiovascular disorders of Graves' disease which have a bearing on the choice of treatment, and also on the outcome The first is that the disorders of the heart in Graves disease are likely to be paroxysmal or transient The auricular fibrillation caused by thyrotoxicosis usually disappears within a few days after thyroidectomy

The congestive heart failure which is caused by toxic thyroid disease is also apt to be transient It is as a matter of fact one of the striking features of the history of heart failure in thyrotoxicosis, that the patient has had repeated attacks of failure without the customary precipitating causes such as effort or infection, and that there have been long periods of remission Such a history of recurring attacks of heart

failure without the usual causative factors is strongly suggestive of thyrotoxic heart failure.

It is also noteworthy that the heart disorders of thyroid disease are reversible to a very high degree. This also applies to the enlargement of the heart in thyroid disease. A large proportion of the cases, particularly the more severe ones, have some enlargement—it is usually mainly a dilatation—and with the cure of the thyrotoxic disease the heart usually returns to its normal size. Even in cases of heart failure with congestion of the most extreme grades, in which patients seem in extremis, and fail to respond to the ordinary forms of treatment, the control of the thyrotoxic disease by thyroidectomy often results in a cure of the heart condition that is to all intents and purposes complete. Such complete cure is very rarely encountered in other forms of heart disease with failure.

The third general characteristic of this group is that thyrotoxic heart disorders are in general more resistant to the common cardiac drugs than similar disorders of other cause. The distinction is not absolute. There are a great many cases of auricular fibrillation due to thyrotoxic disease in which the heart can be slowed readily with the usual doses of digitalis, and there are many cases of heart failure due to thyrotoxic disease which can be satisfactorily controlled with the usual doses of digitalis, but the number of patients who do not respond satisfactorily even to the largest doses is much greater than among individuals with heart disease of other cause.

These, then, are the three outstanding characteristics of the thyrotoxic heart: the transient nature of the disorder, the reversibility of even very severe forms of disorder (failure and enlargement), and the tendency to show a greater resistance to the usual therapeutic measures.

The rapid heart rate of Graves' disease is usually a sinus tachycardia. When it is of the order of 110 or 120 a minute,

it does not require treatment. There are individuals, however, in whom the disease is very active and the rate speeds up to 200 or so a minute, much too fast for an efficient circulation. It is fortunate that this does not happen very often, because we have no direct means of slowing the sinus tachycardia of thyrotoxicosis. Digitalis is of no value. It is often given and in large amounts for sinus tachycardia. All that results after enough of it is poisoning. The heart rate remains fast. Nor does quinidine slow this type of tachycardia. The only way to slow the sinus tachycardia of thyrotoxic individuals is to control the thyrotoxicosis by such measures as the administration of iodine, propylthiouracil, and/or thyroidectomy. In the preparation for thyroidectomy, the heart will slow in a striking manner after suitable doses of iodine. The effect of this treatment is usually temporary. I think it should be regarded essentially as a preoperative measure rather than as a means of maintaining the heartbeat at a slow rate in a thyrotoxic patient. It is rarely possible to keep it slow with iodine alone over periods of more than a few weeks.

The dose of iodine necessary for that purpose is not very large—not very large as doses of iodine are reckoned in therapeutics—but it really represents a great deal of iodine in terms of the amount of iodine in the body. One teaspoonful of the syrup of hydriodic acid daily will slow the heart rate in these cases from 120 or 130 a minute down to normal levels within a period of about a week or ten days. A teaspoonful of hydriodic acid is not usually considered a large dose, but again, in terms of the iodine content of the body, it is a good deal. It contains about 50 mg. of iodine, which represents about twice the amount of iodine present in the body of a normal individual.

As to the treatment of auricular fibrillation in thyrotoxic disease, the workers in this field seem to be in agreement with respect to only one point, namely, that the fibrillation should

be abolished Some wait for spontaneous cessation and others use drugs to abolish it but there is no consensus as to when the fibrillation should be abolished or as to what should be used for that purpose Some depend on digitalis others use quinidine

Some believe that quinidine ought not to be given in auricular fibrillation of the thyrotoxic patients prior to operation and the advice seems to be fairly general in writings on the subject that quinidine should be given after the operation if within a certain period of time the fibrillation does not cease spontaneously How long after? One writer states within 2 days and another advises to wait at least 3 months before quinidine is used

I am not sure what the reason is for the objection to the use of quinidine prior to operation to abolish an attack of auricular fibrillation in a thyrotoxic individual I would like to recommend that in every patient who develops auricular fibrillation as the result of thyrotoxic disease an attempt be made to abolish the fibrillation by quinidine provided the case is without the usual contraindications to the use of quinidine or presents factors which make digitalis more desirable namely complicating mitral disease of long standing or auricular fibrillation which may have been going on for many months or congestive heart failure Perhaps we can have some discussion of this point I know of the argument that quinidine prior to operation often fails to abolish the fibrillation I do not wonder at the failures The doses commonly used are too small The way to use quinidine to abolish auricular fibrillation in these cases is to give 10 grains of the sulfate every 2 hours until the normal rhythm is established or until minor toxic symptoms preclude its further use If the oral doses cause diarrhea similar doses dissolved in propylene glycol may be given intramuscularly

The idea also seems to prevail that the thyrotoxic patient is more sensitive to the toxic effects of quinidine than the

Dr Cattell Dr Eggleston, will you continue the discussion from the standpoint of the patient with hypothyroid disease?

Dr Cary Eggleston This is an aspect of thyroid disease which is not well established There are many who feel that there is no such thing as the myxedema heart as originally described a number of years ago by Zondek, in Germany, and supported in this country very largely by Fahr On the other hand there are many who do feel that there are relatively rare cases in which myxedema is largely responsible possibly wholly so, for cardiac insufficiency There is no satisfactory evidence as yet which permits us to say which of these two groups is correct Personally I think the truth lies between them that there are small numbers of patients with myxedema in whom there is evidence of cardiac failure and in whom adequate control of myxedema may relieve the cardiac failure

It has been noted that in patients who have had myxedema with symptoms of cardiac insufficiency and who have come to autopsy there has been a very high incidence of coronary arteriosclerosis and there are many who feel that it is this process rather than the myxedema which is responsible for the cardiac manifestations

A few years ago as the result of the efforts to reduce basal metabolism as a therapeutic process in reducing the work of the heart the Boston group operated upon a good many patients with heart disease—heart disease of the anginal type and heart disease of other types There was total ablation of the thyroid resulting in a myxedema and reducing the basal metabolism in general to levels below —25 per cent This gave us an opportunity to observe the effects of induced hypothyroidism upon the heart In few or no instances were there any apparent detrimental effects and so far as effects were observed, they were largely beneficial or else of no significance

The manifestations of hypothyroid disorders of the heart

During this period we ask the patient to be up and around because the behavior in bed is no indication of how the patient is going to behave when up and around

If we can, we generally take about two months to bring such a patient to the optimum, and that optimum is not decided by any arbitrary standards of the level of the basal metabolism It is that state, whether it is produced with doses of 30 mg, or 60 mg, or 180 mg, in which the patient obtains relief from symptoms without cardiac distress

Here is an excellent opportunity to take advantage of a natural state, which the Boston group has been producing by operation The patient with myxedema has, in a sense a natural thyroidectomy He can be regulated at the level at which he is comfortable, without previous surgery

I do not have any doubt, Dr Eggleston, of the existence of the myxedema heart, in the sense that the heart rate is slow, the size is generally increased, the circulation is slow, the work of the heart is less, and the PR interval may be prolonged to as much as 0 54 second in some cases With therapy all of these usually revert to normal

I would like to discuss Dr Gold s reference to ' masked Graves' disease We are too often inclined to look for the textbook picture of Graves' disease exophthalmia a rapid heart, a large mass in the neck People in the older age group do not have this typical form of Graves' disease The impression has grown up from work in certain midwestern centers that in the older group we have 2 types of disease toxic adenoma and Graves disease, and that toxic adenoma is merely hyperthyroidism, while Graves disease is something else This notion, to my mind, is erroneous Whenever we see a patient in the old age group who has cardiac disease which does not respond as it should and with no obvious reason for it, we should suspect Graves disease, regardless of the presence or absence of the so called typical picture of Graves disease

Dr Eugene F DuBois Dr Evans and Dr Stewart have been doing a great deal of work on the heart in Graves' disease and myxedema Could we have some remarks from them?

Dr Willis F. Evans The pale, cold, dry skin of patients suffering from myxedema suggested that there might be a decreased amount of blood allotted to the peripheral circulation The peripheral blood flow has now been measured before treatment and on several occasions during the course of thyroid administration in 5 subjects exhibiting the signs and symptoms of this disease In addition, observations of the basal metabolic rate, the circulation time (arm to tongue), the blood pressure, and the pulse rate have been made for correlation with the data relating to peripheral blood flow.

At a time when the basal metabolic rate was low in the myxedematous subjects, the peripheral blood flow was also decreased With increases in basal metabolic rate toward normal, as the result of therapy, there were successive and parallel increases in peripheral blood flow This relationship between metabolic rate and blood flow was linear The pulse rates and pulse pressures of each of the 5 patients showed trends parallel with changes in basal metabolic rates and peripheral blood flow, that is to say, they increased with the giving of thyroid The arm to tongue circulation time was measured by means of Decholin Before treatment the circulation time was prolonged It became shorter during treatment with thyroid

Measurements of cardiac output have not been carried out in these subjects However, Stewart, Deitrick, and Crane made such measurements in a group of myxedematous patients and found that it was low at first, and increased to normal with rise in basal metabolic rate on the administration of thyroid

Studies similar to the ones just reported have been carried out in 18 patients suffering from hyperthyroidism, a disease at the opposite end of the metabolic scale from myxedema In

adjustments require a certain length of time, and the heart would not be immediately fit to carry the increased load.

Dr. Shorr: We are inclined to think that the body is very efficient as a mechanism, and that when things go wrong, very nice adjustments are made, but I think that Graves' disease is one example of where the body falls short. As Dr. Evans pointed out, the various circulatory indices are far in excess of the metabolic need.

It is found that in patients with Graves' disease the arteriovenous oxygen difference is smaller than in the normal. The rapidity with which the blood flows through the capillaries prevents the organism from taking out as much oxygen per unit of time. Does that not indicate that the speed of the circulation is excessive and out of proportion to the needs in the classic case of Graves' disease? It is possible that this overactivity of the circulation does not occur in the older age group. It may be very well worthwhile to study it, Dr. Evans. In these patients the pulse rate is much slower than one would anticipate from the basal metabolism. There is a basal metabolism of +30 or 40 associated with a pulse of 70. I have often wondered whether or not it might be due to the fact that their vegetative nervous system may be less unstable, with less overactivity of the circulation; the arteriovenous oxygen difference would be more nearly normal, and therefore the pulse rate slower. In the young people we find the reverse—the pulse rate rapid, out of proportion to the basal metabolism. Have you any comments on that?

Dr. Evans: That has been our observation; the older individuals with the toxic adenoma certainly have slower pulse rates.

Dr. Janet Travell: I want to [illegible] [illegible]her subject. Dr. Gold spoke about the use of d[illegible] [illegible]cular fibril[illegible] if quinidine failed. Would h[illegible] [illegible]her he give simultaneously, or whether he [illegible] the [illegible] whether he allows an inte[illegible] [illegible]

digitalis Another question Is digitalis ever dangerous in any of the cardiac manifestations or complications of thyrotoxicosis?

Dr Gold It is not well to give large doses of quinidine and digitalis together The two exert a synergistic action which is sometimes hazardous The evidence comes from animal experiments and isolated experiences in man It would take too long to go into the details of the mechanism When one has given very large doses of quinidine without avail, the thing to do is to discontinue for 24 hours because most of the quinidine is eliminated within that period of time, then digitalize the patient as though he had had no quinidine On the other hand, if one gives digitalis first, and in fairly full doses, it is better to wait several days before one gives large doses of quinidine because of the fact that it takes so much longer for the elimination of the digitalis

As to the toxic effects of digitalis in thyroid disease, up to 1916, I think, in this country it was a pretty general practice to give digitalis to most patients with thyrotoxic disease in an endeavor to control the rapid heart rate Many of them were poisoned in that way Out of this arose the belief that digitalis is injurious to the patient already toxic with Graves disease a phenomenon similar to the synergistic effect of two poisons Some have placed the toxic action of the two factors not on the heart but on the brain, resulting in edema of the brain The evidence is far from satisfactory that ordinary digitalizing doses of digitalis exert a greater toxic effect in the hyperthyroid than in the nonhyperthyroid patient

Dr Wheeler I would like to ask Dr Shorr whether he believes digitalis is useful in auricular fibrillation due to Graves disease

Dr Shorr I think there is no difference between Graves disease and any other condition in regard to the indications for the use of digitalis The same factors, auricular fibrillation and failure, are indications for its use, and I believe it has the

thyroid patient to the usual methods of failure therapy are extremely interesting I believe that it is the more generally accepted view that patients with hyperthyroidism who develop failure are likely to be fairly resistant to treatment and that one of the points which leads one to suspect that hyperthyroidism may be the cause of the failure is that one fails to get very far with the usual methods of treatment Would you care to say something else about that?

Dr Stewart Iodine is an essential part of the treatment

Dr Gold As I see it, then, there is no real difference of opinion here if you treat them with iodine at the same time the response of the failure is very good and much the same as that of nonhyperthyroid patients Is that it?

Dr Stewart I think there is too much emphasis on the point that you cannot slow the fibrillator in hyperthyroidism You can slow them down fairly well In many instances even without iodine you can get them down to a fairly low level It may be somewhat higher than the usual level for other patients It may take somewhat more drug than the average dose for an other patient but it can be done I have seen no toxic effects from slowing the ventricular rate in these fibrillators

Dr Eggleston May I speak on that? I believe the reason Dr Stewart has not seen toxic effects is that Dr Stewart is skilled in the use of digitalis We certainly see the toxic effects of digitalis outside an institution such as this We encounter them in consultation where the physician has not known enough about digitalis to handle it as expertly as you or Dr Gold can handle it The average person does not get the slowing in any degree adequate in his estimation to restore a patient unless he uses the iodine nor does the patient s clinical picture change enough to make him feel satisfied so he goes ahead and pushes the digitalis a bit too far I think nausea and vomiting and some of the other toxic symptoms are much commoner outside of teaching institutions than they are here In other words what I am trying to say is that you don t induce

them because you know better, whereas a good many others, not realizing the situation, do induce digitalis intoxication in their efforts to slow the fibrillating or nonfibrillating heart in the presence of an active thyrotoxicosis

Dr John E Deitrick May I take up this point? I will differ with Dr Stewart Consider the patient with auricular fibrillation, a ventricular rate of 140, a basal metabolism of +60, and without iodine I would be greatly surprised if you could lower the ventricular rate more than 10 or 15 beats a minute with digitalis alone, but if you add iodine you can certainly lower it markedly in a week or ten days The iodine, in my experience, is very important I have never been able to control the ventricular rate with digitalis alone At the end of a week or ten days with iodine the digitalis works very well Do you agree with that?

Dr Stewart I think we can show charts where the digitalis alone has caused marked slowing

Dr Gold The difference between these two views may be due to differences in the severity of the disease Patients with extremely high basal metabolic rates, who are very ill, are likely to be more resistant to digitalis than those with milder grades of hyperthyroidism

Dr David P Barr Dr Gold may I make a remark about this? It seems to me that to some extent there has been too much emphasis laid on the strict parallelism between basal metabolic rate and pulse rate In general, there is a surprising correlation, and if you take a group of patients, you will find that the pulse rate increase corresponds fairly closely to the basal metabolic rate increase On the other hand, if you watch an individual patient over a period of time, you will find the greatest variation in the pulse rate I have seen patients who had a basal metabolic rate of +50 and 60 who had a basal pulse of 80 or less, sometimes as low as 75 On the other hand, those same patients in bed on the ward might have pulse rates around 120 to 130 The idea of controlling all the vagaries of

pulse rate in a patient like that with digitalis is like saying that digitalis is going to control the rate of a man who runs a race It cannot be done You cannot make the heart rate come down to the desired level by giving digitalis before the race is run

I would agree with Dr Eggleston that, before we used iodine in these patients with decompensation and regular rhythm, digitalis resulted in almost no slowing at all

Dr Gold How about those with auricular fibrillation?

Dr Barr It also applies to them, particularly if advanced decompensation is present Digitalis often fails to reduce their ventricular rate significantly in the presence of thyrotoxicosis

Dr Eggleston I think *the situation* is analogous to that during active infection During infection the use of heart rate as a guide to digitalization is futile There is the toxic influence which is driving the heart which is more potent than *the effect of the digitalis on the rate*

Dr Gold There is one other point which perhaps we have partly answered, and that is regarding the sensitivity of the hyperthyroid patient to the toxic actions of digitalis It is generally *stated that the patient with Graves* disease is more sensitive to the toxic effects of digitalis than the non Graves patient Is there anything in that, Dr Eggleston?

Dr Eggleston Not in my experience, Dr Gold I think he *responds just about the same as the patient* without Graves disease so far as his likelihood of developing toxic symptoms is concerned

Dr Gold Yet you did say that, by and large, you encounter *more toxicity among patients with* Graves disease treated with digitalis than you do among those who don t have Graves disease

Dr Eggleston I think it is because of the failure to recognize the fact that thyrotoxicosis antagonizes the effect of digitalis on the rate The doctor, using rate as a crude guide pushes digitalis into the toxic range If he followed those patients by some other means the chances are he could avoid toxicity

Perhaps Dr Stewart would say whether the effect on the T wave or on conductivity in thyrotoxicosis could be used

Dr Gold Is there any difference in the tolerance of the Graves patient to digitalis by any method of measurement?

Dr Stewart I don t think so I have not observed any differences, and I don t know of any good experimental work bearing on it

Dr Gold There are, nevertheless, the statements in the literature, made by Plummer and others, warning against the toxic action of digitalis in Graves' disease, especially a toxic action on the central nervous system causing edema of the brain Plummer stated that the patients do badly with digitalis even in the presence of an apparently beneficial action on the heart.

Dr Barr What Plummer showed was that during the period in which patients had been routinely digitalized preoperatively, the mortality from thyroidectomy was higher than it had been in the years when they were not so routinely digitalized On the other hand, it must be remembered that in this series complete digitalization was attempted and that patients received a full dose whether they needed it or not They must have been digitalizing a great number of individuals who would have fallen into the normal range in whom we now believe digitalis may be actually harmful I never felt that that demonstration of Plummer s was any argument against digitalizing a thyrotoxic patient who was decompensated or who had some such trouble as an irregularity of the heart, which might develop into decompensation

Dr Cattell I believe that Dr Gold and Dr Modell have some observations on patients with fibrillation which bear on the problem of slowing in Graves disease

Dr Gold There are two mechanisms by which digitalis slows the heart in the patient with fibrillation One is a reflex increase in vagal tone from the improvement of myocardial

function The other is an extravagal mechanism in which the slowing is due to the direct action of digitalis on auriculoventricular conduction In Graves' disease the reflex mechanism may be inactive Therefore, digitalis can slow the rate only by the remaining mechanism, namely, the direct action on the auriculoventricular conducting system But this requires a very much larger dose, sometimes twice as much as for the "vagal" slowing Such large doses under any conditions are likely to give rise to many cases of poisoning

Dr Cattell The patient with Graves' disease is subject to paroxysms of auricular fibrillation What do we do about that?

Dr Eggleston I used to treat them vigorously I don't any more, because most of those paroxysms seem to be self limited and innocuous If, after subtotal thyroidectomy, the patient continues to fibrillate or if he develops recurrent attacks of fibrillation, I am inclined, provided the patient is still under iodine, to resort to the use of quinidine

Dr Gold Your inclination, then, is not to deal with the paroxysm of fibrillation directly before operation How about a case of this kind A patient is in the ward with auricular fibrillation, being prepared for operation He is going to be there for two or three weeks and during that time he is having attacks of auricular fibrillation once or twice daily They last half an hour or an hour Are you inclined to let him be or would you do something about the attack?

Dr Stewart As you describe it, I would do something If the attacks last long enough, several hours I think I would digitalize the patient in order to reduce the marked changes in ventricular rate even though the heart might still go in and out of fibrillation I do not make any attempt to stop the attacks with quinidine until a certain length of time after operation Even in these cases I also use digitalis at the same time

Dr Eggleston How long do you wait?

Dr Stewart A variable period I usually wait several weeks They sometimes return to a normal rhythm spontaneously in two or three months after operation

Dr Eggleston That brings up a moot point, moot in my mind anyway, as to whether we are running risks of embolism from intra auricular thrombi in the patient who has been allowed to remain too long in fibrillation or who has reverted to sinus rhythm I have my own ideas about that

Dr Gold Let us have them

Dr Eggleston My own ideas are that the transition from fibrillation into a sinus rhythm does not materially enhance the likelihood of embolism

Dr Gold I take it, therefore, that in changing fibrilla tion to normal rhythm, from the standpoint of danger, you regard it as a matter of indifference whether the fibrillation is one day old or five weeks old?

Dr Eggleston Yes

Dr Gold We have here two different answers to the same question Dr Eggleston would use quinidine to control the fibrillation while Dr Stewart would use digitalis

Dr Eggleston Just a minute Dr Gold I think that is sim ply because Dr Stewart and I are answering the same question from two different points of view He was talking of fibrilla tion with heart failure, I think I was dealing with the prob- lem of fibrillation per se without heart failure If there were no heart failure present I would not use the digitalis If there were heart failure I would proceed just as Dr Stewart and use the digitalis

Dr Stewart Whether there was failure or not, I would use digitalis

Dr Gold I think the record is clear on this point We have two different answers to the same question That s common enough So it is also in the literature, some people treat the fibrillation per se, regardless of failure, with digitalis, in the hope of obtaining a slower rate each time the heart goes into

fibrillation, others try to control recurrence of attacks with quinidine

This brings up another point In a patient who is subject to paroxysms of auricular fibrillation with a very rapid rate let us say a ventricular rate of 180 a minute is it your experience that the rate is slower if the patient is kept digitalized?

Dr Eggleston Dr Stewart was just discussing that question

Dr Gold Dr Stewart said yes, but I would like to know what you think

Dr Eggleston Frankly, that has not been my experience

Dr Gold It has not been mine either We digitalize these patients with average doses, and in spite of it, every time an attack of fibrillation pops up, the ventricular rate seems to be as fast as before we gave the digitalis It is probably largely a matter of dosage

Dr Eggleston That has also been my experience

Dr Gold How much quinidine do you give, Dr Eggleston, to prevent attacks of auricular fibrillation in this group of patients?

Dr Eggleston I usually begin with an initial dose of 0 3 Gm *5 times per 24 hours, as evenly spaced* as possible and work from there up until I find a dose which for that patient suffices to control and produces no toxic symptoms You yourself, have mentioned your experiences with very high doses without detriment to the patient I think the drug has to be given with caution, and only on the basis of trial in the individual patient

Dr Gold The fact that the patient has hyperthyroidism presents no special problems?

Dr Eggleston Not in my opinion

Dr Gold What dose of digitalis do you use to control the fibrillation, Dr Stewart?

Dr Stewart If I were going to digitalize I would use 1 8 Gm in 24 hours, and maybe a maintenance dose of 0 2 Gm

As I said in these patients it may take a little more than in other patients

Dr Deitrick Is there any evidence that the heart suffers permanent damage from hyperthyroidism? Does the presence of auricular fibrillation make it necessary to prolong the period of bed rest and iodine in preparation for operation?

Dr Gold You mean structural damage?

Dr Deitrick Yes

Dr Gold Is there any?

Dr Eggleston I wish the pathologists would tell us The clinical evidence is against permanent damage, because even most of these patients who have been in severe congestive failure during hyperthyroidism return to clinically normal individuals following adequate preparatory treatment and adequate subtotal thyroidectomy It seems to be a reversible intoxication rather than structural damage Yet there are statements in the pathologic literature which suggests that there may be some structural damage there The late Dr Ewing some years ago, refused to give me a categoric answer to this question He said that he did not know

Dr Stewart In experimental work with thyroxin feeding to animals, they have not been able to demonstrate any morphologic changes No doubt there must be a functional derangement from which the heart is unable to recover completely, although you are not able to distinguish that heart from another under the microscope

Dr Travell To come back to a point brought up earlier, I believe that Dr Stewart said that he would digitalize a patient and then give him quinidine, isn t that so?

Dr Stewart If I were going to give a patient quinidine, I would slow the rate down first by digitalis

Dr Travell I wonder if there are any dangers in the administration of quinidine to a patient who has received large doses of digitalis?

Dr. Stewart: I don't know of any with therapeutic amounts of digitalis.

Dr. Eggleston: Wasn't it you who brought out that question?

Dr. Travell: It was Dr. Gold.

Dr. Gold: We found that in animals quinidine and digitalis often acted synergistically to produce toxic effects on the heart. After large doses of digitalis, otherwise safe doses of quinidine sometimes caused cardiac standstill.

Dr. Cattell: There is also evidence of antagonism between these two drugs.

Dr. Eggleston: I think certainly that clinical experience does not serve to point strongly to any inherent danger in the simultaneous use or sequential use of these two agents, quinidine and digitalis.

Dr. Walter Modell: Since digitalis tends to maintain auricular fibrillation, isn't that a theoretic objection to its use together with quinidine?

Dr. Eggleston: I think that is purely theoretic. I don't believe it is borne out by clinical experience. In the patients who have been digitalized the sinus rhythm can be re-established just about as well as in those who never had any digitalis.

Dr. Stewart: There is a group of patients who do not respond to quinidine and in whom digitalis will prevent attacks of fibrillation.

Dr. Eggleston: I am very glad you brought that point out, because in theory digitalis should enhance the auricular fibrillation, and there are some patients in whom it does that.

Dr. Gold: I may direct your attention to the fact that a large proportion of the accidents from quinidine reported in the literature occurred in digitalized patients, and also to the few reports of cardiac arrest from quinidine in digitalized patients. I have seen one such case. It resembled the thing we sometimes see in the dog.

SUMMARY

Dr Gold We may now briefly summarize the essential points that have been brought out in the conference this morning

It is perhaps not strictly accurate to regard the cardiovascular disturbances of Graves' disease as complications, but rather as manifestations of the disease, because in the vast majority of cases the heart and the circulation are involved as part and parcel of the complex manifestations of Graves disease itself In some of the cases, particularly the older age group nervous symptoms are at a minimum and the cardiovascular signs outstanding Unless one bears this in mind one is likely to overlook cases of Graves disease These are sometimes referred to as masked hyperthyroidism The clinical problems are heart failure and the common disorders of rhythm, premature contractions auricular fibrillation auricular flutter, and paroxysmal tachycardia The characteristic of these disorders when due to Graves disease is the almost complete reversibility in most cases even in extreme grades The treatment is essentially the same as when these occur in patients without hyperthyroidism However, there is the significant fact that the cause can be attacked through at least the partial cure of the Graves disease itself This is accomplished by the use of iodine propylthiouracil, and subtotal thyroidectomy Most cases require subtotal thyroidectomy after suitable preparation with iodine or propylthiouracil, or both The outlook for medical treatment has improved with the new drug propylthiouracil Cardiovascular disturbances of Graves disease tend to be more resistant to the customary therapeutic agents These patients require more digitalis than most patients to slow the ventricular rate in auricular fibrillation, and often the slowing is not as marked This drug rarely abolishes the auricular fibrillation Its effect in relieving the congestive heart failure of hyperthyroidism is also

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Dr Travell It was Dr Gold

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Dr Gold I may direct your attention to the fact that a large proportion of the accidents from quinidine reported in the literature occurred in digitalized patients and also to the few reports of cardiac arrest from quinidine in digitalized patients I have seen one such case It resembled the thing we sometimes see in the dog

rhythm In the third category, the patients present themselves with a normal rhythm but are seeking advice because of re peated attacks of disordered rhythm of one kind or another The immediate therapeutic problem in these situations is not that of abolishing an attack but of devising a system which will prevent recurrences of whatever kind of attacks the patient is suffering Obviously, these three categories of prob lem are not mutually exclusive, and in many instances one may be confronted with the matter of not only abolishing the attack that is present at the time but of preventing recurrences in one and the same person

I am sure that you are familiar with the common disorders of rhythm but I list them here to make it easier to discuss them (1) premature contractions, (2) auricular paroxysmal tachycardia, (3) auricular flutter, (4) auricular fibrillation, (5) ventricular tachycardia (6) heart block

It is a matter of the greatest importance to establish the pre cise diagnosis, to recognize which one of these disorders of rhythm is the presenting problem When the differential diag nosis is made, it is the unusual case in which one will fail to bring the abnormal rhythm under control by the appropriate application of one or another specific drug In most cases, it is fairly easy to establish the precise abnormal mechanism, but there are cases in which the differential diagnosis is a matter of the greatest difficulty and defies solution even in the hands of the most expert and with the aid of all the special diagnostic devices

We shall not have the time here to go into the details of differential diagnosis If we try that, we shall certainly have no time left for discussing treatment What I should like to do in the two minutes that remain for my introductory remarks is to point out what I believe to be the best procedure in the case of a patient presenting a paroxysm of rapid heart action, whether it be regular or irregular, and in which we do not have the means for establishing the precise abnormal mecha

Management of Disorders of Cardiac Rhythm

Dr J James Smith The internist and the cardiologist spend a good deal of time on the subject which is to be discussed in the conference this afternoon, namely, the management of disorders of cardiac rhythm The opening remarks will be made by Dr Gold

Dr Harry Gold I should like to suggest that we consider the treatment of disorders of cardiac rhythm under three separate headings First, there is the treatment of the patient with a chronic or persistent disorder of rhythm, for example the case of persistent auricular fibrillation or flutter, or heart block Second, there is the problem of the acute attack of disordered rhythm such as the paroxysm of auricular fibrillation auricular flutter, auricular tachycardia, ventricular tachycardia, or heart block The third problem is the prevention of recurrences of attacks in patients with paroxysmal disorders of rhythm

The problems of therapy are quite different in these three categories For example, in the patient with chronic auricular fibrillation, one rarely aims at abolishing the abnormal rhythm One usually tries merely to slow the ventricular rate to normal levels and allow the patient to carry on with the auricles in fibrillation In the second category, the patients present themselves in the midst of an attack of disordered rhythm, let us say, an attack of auricular fibrillation They may give a history of having had previous attacks, but whether they do or not, the problem before you at the time is that of abolishing fibrillation of the auricles and restoring a normal

paroxysm of auricular tachycardia within a period of a few minutes and it may do so with complete safety, whereas the oral doses of quinidine may take hours to achieve the same result, and the intravenous injection of quinidine is very risky except in the hands of those who have had a good deal of experience with its use in that way I will ask you to bear in mind that the suggestion which I have made concerning the use of quinidine applies only to those circumstances in which the patient has developed an ectopic rhythm and in which for one reason or another, the precise nature of the ectopic rhythm is not determined I hope that the discussion will make clear the best measures for cases in which the contrary *is true, namely, the precise nature of the disordered* rhythm is established

Dr Smith Dr Stewart, would you care to take up the discussion at this time?

Dr Harold J Stewart Those of us who see a large number of cases of paroxysmal disorders of rhythm find that nodal tachycardia is one of the most common This and auricular paroxysmal tachycardia are grouped under the term supraventricular tachycardia The two are treated similarly

I was amazed to hear that a paroxysm of auricular fibrillation would need to be treated without a clinical diagnosis Most of these cases have such a rapid ventricular rate that a large pulse deficit results, and the physician should be able to make a correct diagnosis In auricular flutter, one often sees the flutter waves in the neck veins when the patient lies flat and the veins fill up The examiner is often able to estimate the ratio of the number of flutter waves to the number of ventricular beats In paroxysmal auricular tachycardia, the rhythm is regular and the rate is constant, while in ventricular tachycardia, one can hear a little whirr which indicates a slight irregularity, and every now and then a large wave is seen in the jugular vein in the neck when the auricles and ventricles contract simultaneously In short, the physician ought to be

nism at work Specifically, assume that a patient presents himself to you with an attack of rapid heart action regular or irregular, and suppose that with the methods available at the time you cannot determine whether the problem is one of frequent premature contractions, auricular tachycardia auricular flutter, auricular fibrillation, or ventricular tachycardia This is a situation in which the general practitioner finds himself not infrequently Now assume that you wish to *terminate the abnormal rhythm What should you do?* What treatment would provide the best chance of bringing the abnormal rhythm under control without appreciable risk? My suggestion is the use of quinidine Give the patient 0 6 Gm (10 grains) of quinidine sulfate every 2 hours and examine the heart before each dose Continue the medication until the attack comes to an end or until the patient develops symptoms of intolerance such as those of cinchonism (blurred vision tinnitus, impaired hearing) or gastrointestinal symptoms (nausea, vomiting diarrhea) These minor toxic effects preclude the further use of the drug The 2 hour interval is chosen because the maximum effect of *any one dose* usually develops in this period of time If the first dose has caused no *minor toxic effects the next dose of 10 grains* is not likely to produce serious toxic effects The object is to build the effects of one dose on the effects of the previous one until a level is reached in the body sufficient to terminate the abnormal rhythm Here is one drug which provides a good chance of bringing under control a fairly large proportion of the cases of any one of 5 different disorders of cardiac rhythm

Of course we are much better off if we are *in a position* to establish the exact nature of the abnormal rhythm before *treatment is started That is so* because quinidine is not the best choice for all of these 5 disorders For example an intravenous injection of 3 U S P units of an appropriate digitalis preparation, such as ouabain or Cedilanid or digoxin repeated in 15 to 30 minutes if necessary, may terminate a

to induce vomiting Finally, if these measures have not proved effective, the patient is digitalized This usually terminates the paroxysm promptly We have found an intravenous dose of 0 8 to 1 6 mg of lanatoside C effective for this purpose One drug which should not be used in paroxysmal auricular tachycardia is morphine, if the patient has recurrent attacks, morphine addiction may result

In auricular flutter, we have also found digitalis most effective It is our practice to digitalize the patient, and it is our experience that it may take more than the usual therapeutic dose of this drug to restore the normal rhythm If digitalis proves ineffectual after a suitable trial, quinidine may be tried, and in a few instances this will restore the normal rhythm

It is our experience that, in many cases of paroxysmal auricular fibrillation with rapid ventricular rate, the abnormal rhythm ceases spontaneously when the patient is put at rest and kept quiet. If, however, the abnormal rhythm persists and its prompt termination is indicated, we usually give digitalis to slow the ventricular rate The normal rhythm might then return, but, in the event that the auricular fibrillation still continues, quinidine may be used to terminate it

[EDITOR Since this conference was held experience has been acquired with procaine amide hydrochloride (Pronestyl) in ventricular tachycardia These supplementary remarks have been supplied by Dr Stewart

The new compound has been found effective in terminating ventricular tachycardia, and it does so rapidly after intravenous injection of 200 mg per minute in total doses of 200 to 1,000 mg The drug frequently lowers the blood pressure and it is well to take the pressure during its administration The results are maintained by doses of 0.5 Gm every 4 hours for a few days An oral dose of 1 0 Gm followed by 0 5 Gm every 4 hours is also effective The drug by the oral route has little effect on the blood pressure More experience is necessary to establish the place of this drug in the treatment of disorders of cardiac rhythm]

able to arrive at a diagnosis in many cases of paroxysmal disorders of rhythm, without electrocardiographic aid, before treatment is started. Good medical practice requires, under most circumstances, that one should know what the condition is before one treats it. Many physicians have portable electrocardiographic machines and carry them along when they go out to see a patient in whom there is the emergency of an abnormal rhythm.

I agree that, if one does not know the nature of the paroxysm, quinidine would be safer than digitalis. It is not likely to do any harm in several of the disorders of rhythm, whereas digitalis could do harm if the rhythm turned out to be ventricular tachycardia.

When the precise nature of the abnormal rhythm is known, the measures which may be used are fairly specific. For a paroxysm of auricular or nodal tachycardia, digitalis is, in our experience, more effective than quinidine. First it is well to try simple measures such as having the patient take a deep breath and hold it, the Valsalva experiment, or have the patient gag himself, and if the patient is not too ill, nausea may be induced, and these frequently terminate an attack. If these measures are not effective, carotid sinus pressure may be applied, but in this case atropine ought to be at hand ready to use in case the carotid pressure causes prolonged cardiac asystole. The carotid pressure is applied first on one side, then on the other, and finally on both sides simultaneously, if necessary. We have seen attacks terminated by the additive effect of carotid sinus pressure while the patient is taking a deep breath. Occasionally, we use Mecholyl subcutaneously in doses of 20 to 30 mg. in young individuals, and 30 to 50 mg. in older individuals. Here also, atropine ought to be ready at hand before the Mecholyl is given, and it should be injected at once if the patient shows any idiosyncrasy to the Mecholyl. Mecholyl is a dangerous drug. It causes many side effects. We do not use it very often. Occasionally, we use apomorphine or ipecac

the thumb and presses the artery back against the muscle mass of the vertebral column, one is more likely to secure an effective stimulus This should be done first on one side, and then on the other Sometimes the pressure on one side, sometimes on the other, will terminate a paroxysm of auricular tachycardia In the case of auricular flutter, the carotid pressure does not result in a cessation of the flutter, but in a marked slowing of the rhythm for a few beats

Something should be said about the advisability of giving quinidine to patients in whom an attack of auricular fibrillation has persisted for some days As Dr Gold has suggested, one should hesitate to use quinidine in auricular fibrillation of long duration After a certain time, and particularly if heart failure has developed, thrombi appear in the auricles and these may become emboli when the auricles begin to contract with the restoration of the normal rhythm It is of course true that the same occurs in patients who spontaneously return to normal rhythm, but then, one cannot help that In a patient in whom an attack of auricular fibrillation has lasted for 48 hours it is inadvisable to use quinidine In such a case, it is best to use digitalis first in sufficient amounts to slow the ventricular rate to the normal range, allowing the fibrillation of the auricles to continue

A word about the paroxysm of ventricular tachycardia This is the most difficult one to terminate It often resists the various measures to which other tachycardias respond Quinidine in adequate doses should be the first choice Magnesium sulfate is sometimes useful in ventricular tachycardia An intravenous dose of 20 cc. of a 10 or 20 per cent solution of magnesium sulfate will sometimes terminate an attack of ventricular tachycardia when other measures have failed

Dr Cary Eggleston Virtually all the effective and useful measures for controlling the paroxysmal disorders of rhythm have already been mentioned In the light of Dr Gold's opening remarks, I may draw attention to the fact that, in the

The students should be reminded that complete heart block and bundle branch block are contraindications to the use of quinidine.

Dr. Smith: For several days I have been trying to find some one who has had some experience with intravenous procaine in disorders of cardiac rhythm. It has been like trying to find a man who has voted in a Gallup Poll. It seems as though the anesthetists are a jump ahead of us in this matter. I hope we may have some discussion of that subject.

Dr. Pardee, would you care to make some remarks?

Dr. Harold E. B. Pardee: I agree with Dr. Stewart in the matter of diagnosis. I should hate to think of a situation where one could not make the differential diagnosis between auricular fibrillation and a paroxysm of auricular tachycardia. All one has to do is to listen to the beat of the heart; one is totally irregular, and the other is perfectly regular. The rate in a paroxysm of auricular fibrillation may be very rapid, perhaps 180 per minute, but as one listens carefully one perceives phases in which the rhythm falters. That does not occur in a paroxysm of auricular tachycardia.

Dr. Stewart referred to the variations in the rhythm of patients with ventricular tachycardia. In my experience, this irregularity seems to be much talked about, but rarely seen in the records. Slight irregularity is occasionally seen in the rhythm of ventricular tachycardia, but it is certainly not a characteristic of this disorder.

I want to say a word about carotid pressure, not as a method for treatment but as a method for diagnosis. It is very useful in diagnosis. In auricular flutter, carotid pressure will usually slow the heart, especially if the patient has not had quinidine in amounts sufficient to block the vagal mechanism.

The technic of the carotid pressure needs to be carefully performed. It is not enough to press on the carotid artery. Unless it is properly done, the carotid sheath is merely pushed behind the larynx and the pressure is not effective. If one uses

the patient be near or remote from the office The patient should be urged to get to the office or a hospital, or a laboratory, and have an electrocardiogram taken at once I might add that one cannot always be certain of the diagnosis even with an electrocardiogram, although it is usually very helpful Once the diagnosis is established, one can select rational therapy

I would like to add to the remarks made on carotid sinus pressure It is wise to have the patient lying down during carotid sinus pressure, because every once in a while this procedure will cause syncope I agree with Dr Pardee s comments on the technic. I have seen a good many patients in whom the so-called carotid sinus pressure was tried without avail because it was so imperfectly carried out

The use of digitalis to terminate an attack of auricular tachycardia has already been mentioned This drug is also useful in preventing recurrences We can very often carry the patient along satisfactorily for protracted periods of time by the use of fairly large doses of digitalis We have one patient attending our clinic here, who used to be incapacitated by these attacks, and now the patient comes in merely for routine check with the statement that the paroxysms of auricular tachycardia are only occasional very brief, and not particularly troublesome

The danger of emboli resulting from the termination of paroxysms of auricular fibrillation has been mentioned I have not seen any serious embolic phenomena under these conditions This may merely be a difference of experience in the case of two men I highly respect Dr Pardee s opinion on this matter It has been frequently emphasized that it is inadvisable to terminate a paroxysm of auricular fibrillation by means of quinidine, if it has endured for any considerable length of time Perhaps it is merely good fortune on my part, but I have never seen a disaster from bringing such an attack to an end

majority of cases, the situation is not one of grave urgency Of course, it is our desire always to give the patient relief as promptly as possible, but, within the range of my experience there is time in most instances to analyze the patient's condition fairly thoroughly and to determine the precise nature of the mechanism involved

I think the greatest problem is presented by those patients who come to the doctor with a history of recurrent attacks of severe palpitation By questioning these patients one will sometimes unearth a history that permits one to hazard with reasonable accuracy, a diagnosis as to the probable mechanism Statistics are helpful in this regard We know that the auricular form is far more common than any other form of paroxysmal tachycardia It gives rise to a regular rhythm The patient is usually able to sense the difference between the regular and irregular rhythm Our major problem lies in the group in which the patients seek relief from possible future attacks, and in which we lack adequate information for a precise diagnosis As Dr Stewart has mentioned I also think that digitalis is very effective in the control of auricular paroxysmal tachycardia, it is less effective in the nodal form However, I agree with Dr Gold's opening remarks that, *in a case where the diagnosis cannot be made with certainty, we should probably resort to quinidine*

I mentioned the fact that in the majority of cases the paroxysms of abnormal rhythms do not present urgent problems but there are times when the situation is one of immediate urgency For example, the patient may black out, as he calls it in these attacks This reaction is more likely to occur at the onset or possibly at the termination of an attack than at any other time, in my experience In many cases we *have* just got to take our chances and try quinidine We inform the patient that *it is imperative to have an* electrocardiogram made at the time of the next attack no matter what the circumstances, whether it be during the day or night, whether

procaine injected intravenously effective in abolishing various ectopic rhythms occurring in the course of thoracic surgery. There is the fact that these patients were anesthetized, and such doses of procaine may be safer in anesthetized individuals than in others We need more experience in relation to the dosage of procaine It seems to me quite worth while to pursue observations on procaine in this connection

I think this a proper time to discuss the various comments which have been made on my opening remarks I am glad to see that there is no disagreement with my general thesis, namely, that quinidine is the drug of choice in all of 5 disorders of cardiac rhythm under certain conditions, those being, that in the particular case a decision has been reached that the normal rhythm should be restored as quickly as possible, and that the case is one in which the differential diagnosis with respect to the precise mechanism at work has not been made The failure to establish the precise mechanism may be due to several factors either the available facilities are not adequate, or the physician is a general practitioner without sufficient experience to enable him to differentiate them, or the physician is an expert in these matters but, in spite of all the measures for differential diagnosis, is still unable to arrive at a precise diagnosis

Most of the comments which appear to be in disagreement relate to a matter which I had hoped would be omitted in this conference, namely, differential diagnosis, in order to leave us time to explore more fully the items of treatment Obviously, that would require certain assumptions, namely, that the diagnosis had been established or that a final decision concerning the diagnosis cannot be reached Dr Stewart indicated that the differential diagnosis between these disorders of rhythm is easy to make, and he expressed amazement that one would be [illegible] to establish the diagnosis of a p[illegible] n by clinical means, also [illegible] cardia I must admit that

of those in whom the attempt to restore a normal rhythm should be made

There are figures indicating that the incidence of emboli is higher in patients with auricular fibrillation lasting a year or more than in those in whom a normal rhythm is restored. The evidence, however, is not conclusive, because there may have been selection of cases, and those in whom the auricular fibrillation persisted may have been patients with more advanced disease

Dr Smith referred to the recent case in which an attempt to abolish a paroxysm of ventricular tachycardia resulted in a complete auricular standstill This occurred after about 2 5 Gm of quinidine Yet, according to Dr Gold that is not an excessive amount of quinidine It was given in fractions at intervals of 2 hours

Dr Gold Was that 0 4 Gm every 2 hours?

Dr Deitrick Yes, and the patient developed a complete auricular standstill This was temporary and was followed by the restoration of a normal rhythm

I might add one word about nodal tachycardia I find it very difficult to control Some of you may recall the patient here at the New York Hospital last year and the difficulties encountered in his management I wonder whether there is any better treatment than digitalis to terminate a paroxysm of nodal tachycardia I would like to ask Dr Gold whether quinidine has any effect on the A V node

Dr Smith Dr Gold, maybe you are going to answer my question on procaine

Dr Gold I have had no direct experience with it but there is good experimental evidence showing that procaine has a quinidine like action on the myocardium so that one might expect results similar to quinidine There is the question of its dangers, and that has not been sufficiently established Dr Burstein published a report in the March 1946 issue of *Anesthesiology* in which he found 30 to 70 mg of

proper I should be the last one to recommend the treatment of disorders of cardiac rhythm without at least an attempt at a precise diagnosis but I have had enough experience to make me aware of the rather wide gap between an attempt and success in this problem What I wished to emphasize was the fact that in a large proportion of these cases the patient does not have to go without specific and effective treatment even though a precise diagnosis is not made

I agree with Dr Eggleston that many of these paroxysms of ectopic rhythm do not present urgent situations and every effort should be made to establish the precise mechanism not only for the purpose of using the most effective method of treatment for the current attack but to prevent repetitions One can of course argue that if the situation is not urgent and the diagnosis cannot be made one merely sits by until the attack subsides spontaneously It is very likely to do so after minutes or hours or days in the majority of cases In fact most patients present themselves with a history of previous attacks which did subside spontaneously and that is the meaning of the term paroxysmal ectopic rhythm We must leave it to the judgment of the physician to decide whether it is important or imperative to terminate the attack as quickly as possible As Dr Eggleston pointed out these attacks sometimes give rise to a black out There are other urgent problems Some patients who never had anginal symptoms before will develop a severe attack of substernal pain radiating to both arms the wrists and the back so that one is left uncertain at the time whether an acute coronary thrombosis gave rise to the etopic rhythm or whether the ectopic rhythm gave rise to an attack of coronary insufficiency There are also patients in whom the circulation deteriorates as the rapid abnormal rhythm continues and it is not long before shortness of breath pulmonary rales and even pulmonary edema supervene That is why I urge that the physician have a medication at his

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an expert will arrive at a fairly sound hunch within a few minutes by clinical means with the aid of the electrocardiogram and carotid sinus pressure But I must also add that the expert who has carefully analyzed both his successes and failures in differential diagnosis will not feel particularly secure in his decision in a great many cases Dr Deitrick's reference to the 181 cases at Bellevue Hospital last year is of interest in this connection In this series, 5 cases were labeled supraventricular tachycardia' What is the meaning of such a diagnosis? Does it not mean that in nearly 3 per cent of all the cases, they were unable to decide what ectopic rhythm the patient had? The term supraventricular tachycardia' is commonly applied to an abnormal rhythm in which the electrocardiogram shows an essentially normal ventricular complex, but in which one cannot determine the nature of the auricular activity When one can determine it, one does not use a term which indicates merely that the pacemaker is somewhere above the ventricle, but labels the condition sinus tachycardia, auricular tachycardia, nodal tachycardia, or auricular flutter As Dr Eggleston stated, the most rational and most effective treatment is possible only when these precise diagnoses are made Here then is the failure to make the exact diagnosis in 1 of every 10 cases with a regular abnormal rhythm in the hands of experts in an outstanding hospital with all the facilities for establishing the diagnosis Consider, therefore, how much worse the situation may be in the case of the country doctor *who may have no electrocardiograph*, or may be less familiar with the use of the carotid sinus pressure during the taking of the electrocardiogram, as well as with the special features of the tracing which enable one to distinguish several of these disorders of rhythm

In my opening remarks, I described the treatment which is best under these conditions The plea for establishing the mechanism of the abnormal rhythm is, to be sure, quite

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disposal for immediate use, especially in such cases, even if he remains in some doubt as to the exact nature of the ectopic rhythm, and it is for this purpose that I have recommended the quinidine

Let me come back for a moment to the matter of distinguishing the different forms of disordered rhythm Both Dr Pardee and Dr Stewart indicated that it would be quite remarkable if a fellow could not distinguish clinically a paroxysm of auricular fibrillation from one of auricular tachycardia I agree that in this case an error should be very infrequent, but on the other hand, how about the case of auricular flutter with a varying block? Can we be so sure about distinguishing this from auricular fibrillation by clinical means? There are also cases of premature contractions appearing in large numbers and at irregular intervals which are extremely difficult to distinguish from auricular fibrillation I remember a striking experience many years ago in the clinic of Dr John Wyckoff He was an expert in these matters He then believed that the condition of frequent premature contractions was a precursor of auricular fibrillation He showed us a patient with large numbers of premature contractions and predicted that one of these days we would find her in auricular fibrillation Several years later, he gathered a group of us at the clinic to listen to this patient, and said that now she had auricular fibrillation as he had predicted she would have Her heartbeat certainly sounded like auricular fibrillation An electrocardiogram was then taken and there she was with the same old condition, extremely frequent auricular premature contractions Since then I have encountered many similar problems in differential diagnosis There is still another condition, namely, that of a paroxysm of auricular fibrillation with bundle branch block In some, the patient s normal rhythm shows a bundle branch block, and in others the bundle branch block develops as a result of the rapid

rhythm of auricular fibrillation I have rarely seen a case of this kind in which the error of calling it a ventricular tachycardia was not made Such a tracing with a diagnosis of ventricular tachycardia was brought to my office from the Pediatrics Department this very afternoon There was no doubt of the error, it was a case of auricular fibrillation with a bundle branch block Bundle branch block may complicate any of the supraventricular tachycardias, and to distinguish these from ventricular tachycardia is a matter of first importance, for, if it is a paroxysm of auricular tachycardia with bundle branch block, a large intravenous dose of a digitalis preparation may terminate the attack within a few moments but one would certainly not give digitalis to terminate a ventricular tachycardia because, first, it will fail to do so, and second, it might precipitate the disaster of ventricular fibrillation Dr Pardee spoke about an irregular rhythm in ventricular tachycardia as a condition much talked about but rarely seen in the electrocardiogram That is also my experience I have often wondered whether most of the cases presented as ventricular tachycardia with an irregular rhythm are not in fact cases of auricular fibrillation with a bundle branch block

Dr Deitrick s remark on the necessity of considering the underlying cardiac state in patients with disordered rhythms is very well taken An acute disorder of rhythm is a dramatic event, and may engage our attention to the exclusion of more important problems in the particular case I have seen doctors preoccupied with the paroxysm of auricular tachycardia and overlook the fact that it was caused by an acute coronary thrombosis or preoccupied with the repeated attacks of auricular fibrillation and overlook an underlying Graves disease with predominant cardiac symptoms

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Dr. Deitrick's remark on the necessity of considering the underlying cardiac state in patients with disordered rhythms is very well taken. An acute disorder of rhythm is a dramatic event, and may engage our attention to the exclusion of more important problems in the particular case. I have seen doctors preoccupied with the paroxysm of auricular tachycardia and overlook the fact that it was caused by an acute coronary thrombosis, or preoccupied with the repeated attacks of auricular fibrillation and overlook an underlying Graves' disease with predominant cardiac symptoms.

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disposal for immediate use, especially in such cases, even if he remains in some doubt as to the exact nature of the ectopic rhythm, and it is for this purpose that I have recommended the quinidine.

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tachycardia is still present, unless a check is made with the electrocardiogram There is much more to the expert management of an attack of ventricular tachycardia, but this plan avoids one of the major sources of risk

Dr Smith Dr Stewart, are there any comments you would like to make in relation to Dr Gold s remarks? Perhaps you might wish to say something about the treatment of the case of ventricular tachycardia which fails to respond to quinidine, and what to do for ventricular tachycardia that sometimes occurs as a result of digitalis poisoning

Dr Stewart Supraventricular tachycardia with bundle branch block has been reported in the literature I do not know how many such cases there are, but they are so rare that the confusion of this condition with ventricular tachycardia is not likely to be a source of any considerable trouble

In regard to the use of large doses of quinidine, one should bear in mind the danger of so poisoning the heart as to suppress the sinus node In such a case, if the ventricular tachycardia is terminated, the outcome may be fatal

I might mention my experiences with cases of pericardiectomy for constrictive pericarditis, which were performed by Dr Heuer and Dr Andrus Frequent electrocardiograms were taken during the procedure, and paroxysms of abnormal rhythm were often seen as the result of mechanical stimulation, but they ceased immediately when the surgeon gave the heart a rest

Many of you will recall the patient here in New York Hospital, who had a variety of abnormal rhythms The attacks of nodal tachycardia were the most difficult to control in this case In the several years of observation of this patient, during which she showed various abnormal rhythms, it sometimes seemed that digitalis was effective in preventing attacks over a long period of time, and sometimes quinidine in maintenance doses seemed to prevent the paroxysms

When a patient receives quinidine daily over long periods to prevent recurrences of paroxysms of tachycardia, an electrocardiogram should be taken from time to time to find out whether there is any widening of the QRS This, I believe, is the only evidence of quinidine poisoning which one might be able to discover early

Dr Smith I should still like to have an answer to my question on the treatment of ventricular tachycardia which fails to respond to quinidine, and the question on what to do for ventricular tachycardia which occurs in digitalis poisoning

Dr Stewart It is rare that quinidine fails to abolish ventricular tachycardia when the drug is used in adequate amounts If it is urgent to stop the ventricular tachycardia, for instance, in the patient with a recent coronary occlusion, it is my practice to start quinidine at once without delaying to test for idiosyncrasy to quinidine I give 0 4 Gm and repeat this every 4 hours I do not give it at intervals of 2 hours In most cases the abnormal rhythm is abolished with total doses up to 2 4 Gm on the first day If this proves insufficient, the dose may be increased by 0 4 Gm the next day, and again by still another 0 4 Gm on the third day One should be on careful watch for toxic effects

In the group of patients mentioned by Dr Smith, who have been digitalized, ventricular premature contractions may or may not be present and then if quinidine is given, many ventricular premature contractions may be produced There are reports in the literature to the effect that quinidine and digitalis together caused ventricular tachycardia, the beats arising alternately from the two ventricles Most of these terminated fatally There is really not much that one can do in such cases If the quinidine is continued, ventricular fibrillation may ensue and this is usually fatal It is well to discontinue both drugs Procaine may find a place in the treatment of this toxic effect

Dr Eggleston May I make a remark on the paroxysms of

auricular fibrillation which occur in thyrotoxic patients? I have not found anything which controls these paroxysms except therapy for the correction of the hyperthyroidism iodine, thiouracil and related compounds or surgery Neither quinidine nor digitalis is effective in preventing the paroxysms of auricular fibrillation until the hyperthyroidism has been brought under control

Dr Gold I should also like to make a few supplementary remarks at this point Dr Stewart stated that bundle branch block so rarely complicates a supraventricular tachycardia or a paroxysm of auricular fibrillation, as to present little or no problem in differentiating these from ventricular tachycardia I encounter that problem not at all infrequently, and I wonder whether the view that it is a rarity does not arise from the very fact that the problem is not commonly considered, and an erroneous diagnosis of ventricular tachycardia *is made As I have already mentioned most of these* cases which I have seen *were erroneously labeled ventricular* tachycardia

A further word on the dosage of quinidine seems to me worthwhile Suppression of the sinus node during the use of this drug in ventricular tachycardia, or in the case of any other ectopic rhythm for that matter, is not necessarily the result of improper dosage One cannot say that, in a particular case, the ventricular tachycardia would necessarily *have been abolished without the auricular standstill* if smaller doses had been used for in some of these cases, as the drug is continued the electrocardiogram may reveal a marked slowing of the idioventricular rhythm from let us say, 200 to 120 a minute but, even in the tracing showing the slow rate the mechanism may still be that of ventricular tachycardia without P waves as evidence of auricular standstill This simply means that in some cases of ventricular tachycardia, the level of quinidine action necessary to abolish the idioventricular rhythm is sufficient to abolish the ac

tivity of the auricles, and that if smaller doses were given, the auricular activity would not be suppressed, but then also the ventricular tachycardia would not be abolished It is simply a matter of good fortune that, in the majority of cases, sufficient differential in the sensitivity of the two structures to quinidine exists, so that it is possible to arrest the idioven tricular pacemaker without inactivating the sinus node The method I described for controlling ventricular tachycardia helps to ensure against suppressing both auricular and ventricular activity at the same time by quinidine

There is another point about quinidine dosage and the like lihood of successful control of an ectopic rhythm A large proportion of the failures to abolish an abnormal rhythm by means of quinidine are due to inadequate dosage If we pursue the plan of giving a dose of 0 4 or 0 6 Gm at intervals of between 2 and 4 hours, and continuing that system until either the ectopic rhythm is brought under control or minor toxic effects, such as disturbing symptoms of cinchonism, vomiting, or diarrhea, appear, the number of failures will be greatly reduced In the vast majority of cases which have come to my attention as failures, the drug was simply discontinued after a period of arbitrary dosage unrelated to either therapeu tic or toxic effects

Dr Stewart referred to the widening of the QRS wave as evidence of quinidine toxicity and stressed the need of an electrocardiogram taken from time to time, which might show this effect, in patients who receive quinidine daily over long periods I believe this is a useful device for avoiding more serious poisoning We studied this phenomenon several years ago and found that daily doses of the order of about 2 Gm may prolong the QRS time by about 20 or 25 per cent Some patients are much less sensitive, and larger doses may be given before this effect occurs It does not seem wise to increase the dose of quinidine beyond that which prolongs the QRS time by 25 per cent above the control for that person, although it

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on the A V node Since the existence of such a block is masked in the electrocardiogram showing a ventricular tachycardia, it seems to me wiser to refrain from using quinidine or any other drug to abolish the ventricular tachycardia caused by digitalis poisoning It is probably the lesser of the two evils to allow the ventricular tachycardia to continue until it disappears spontaneously as the elimination of the digitalis takes place

Dr N T Kwit In regard to the dose of Mecholyl, I was surprised to hear that the range of doses for younger people was lower than that for older people I would have expected the reverse since older people are so much more likely to have coronary disease which is sometimes stated to be a contraindication to the use of Mecholyl I recall an experience in which a man 50 years old developed a paroxysm of auricular tachycardia for which I used Mecholyl He had never complained of angina of effort, but after a dose of 50 mg subcutaneously, while the attack subsided, he developed a terrifying attack of substernal pain

Dr Walter Modell It has been stated here that digitalis is effective in abolishing a paroxysm of auricular tachycardia, and that the drug may also be continued to prevent recurrences I believe I once heard Dr Gold mention some tricks for increasing the efficacy of digitalis in a paroxysm of auricular tachycardia and auricular flutter

Dr Smith What are they?

Dr Gold In a paroxysm of auricular tachycardia, one is likely to use digitalis only after the various devices which have already been described have failed The point I have in mind is based on the fact that digitalis increases the sensitivity of the heart to carotid sinus pressure Inject 0 3 mg ouabain intravenously and wait about 30 minutes Now carotid sinus pressure may terminate the attack abruptly If the dose of ouabain turns out to be too small for the particular patient, the tachycardia may return within a few minutes In that event, one

is possible that one can produce even greater QRS prolongation without serious consequences In this connection, perhaps we should call attention to the fact that, if a patient receives a fixed daily dose for about 5 days, and at the end does not show this effect, it is not necessary to take any more electrocardiograms later This is so because quinidine cumulation, like that of many other drugs, is a self limiting process, and all cumulation of quinidine that is going to take place with a fixed daily dose does so during the first 4 or 5 days Therefore if a particular effect has not taken place by that time, there is little likelihood of its occurring later.

In relation to Dr Smith's question as to how to treat ventricular tachycardia which is not controlled by quinidine even when the drug has been given to the point of toxic effects, the earlier comment by Dr Pardee may be recalled An intravenous dose of magnesium sulfate, 10 or 15 cc of a 10 per cent solution, is sometimes quite effective An intravenous dose of procaine might also be tried, but with this I have had no experience

[Editor See remarks on Pronestyl above]

Dr Smith has also asked about ventricular tachycardia due to digitalis poisoning I would suggest that no attempt should be made to terminate this by any drug In experiments on animals which were published several years ago, we found quinidine very effective in terminating the ventricular tachycardia induced by digitalis It was usually a fleeting effect and seemed to be a result not only of direct action on the ventricle, but also a result of the fact that the sinus node was so much accelerated as to make the auricular activity faster than the idioventricular activity A source of serious danger appeared in these experiments namely, the fact that ventricular arrest often occurred due to the fact that the dose of digitalis which had poisoned the heart sufficiently to induce ventricular tachycardia had also produced complete block by its direct action

on the A V node Since the existence of such a block is masked in the electrocardiogram showing a ventricular tachycardia it seems to me wiser to refrain from using quinidine or any other drug to abolish the ventricular tachycardia caused by digitalis poisoning It is probably the lesser of the two evils to allow the ventricular tachycardia to continue until it disappears spontaneously as the elimination of the digitalis takes place

Dr N T Kwit In regard to the dose of Mecholyl I was surprised to hear that the range of doses for younger people was lower than that for older people I would have expected the reverse since older people are so much more likely to have coronary disease which is sometimes stated to be a contraindication to the use of Mecholyl I recall an experience in which a man 50 years old developed a paroxysm of auricular tachycardia for which I used Mecholyl He had never complained of angina of effort but after a dose of 50 mg subcutaneously while the attack subsided he developed a terrifying attack of substernal pain

Dr Walter Modell It has been stated here that digitalis is effective in abolishing a paroxysm of auricular tachycardia and that the drug may also be continued to prevent recurrences I believe I once heard Dr Gold mention some tricks for increasing the efficacy of digitalis in a paroxysm of auricular tachycardia and auricular flutter

Dr Smith What are they?

Dr Gold In a paroxysm of auricular tachycardia one is likely to use digitalis only after the various devices which have already been described have failed The point I have in mind is based on the fact that digitalis increases the sensitivity of the heart to carotid sinus pressure Inject 0 3 mg ouabain intravenously and wait about 30 minutes Now carotid sinus pressure may terminate the attack abruptly If the dose of ouabain turns out to be too small for the particular patient the tachycardia may return within a few minutes In that event, one

may safely repeat the dose of ouabain and the carotid sinus pressure This technic frequently makes it possible to abolish a paroxysm of auricular tachycardia with smaller amounts of digitalis Any of the intravenous injectable digitalis preparations may be used for this purpose, although the more rapidly acting ones are more practical

[EDITOR In connection with rapid acting digitalis materials, a paper recently appeared in the *Journal of Pharmacology and Experimental Therapeutics* on the ester, acetyl strophanthidin The intravenous injection of this compound produces the full cardiac effect in about 15 minutes, and the effect wears off in a few hours It should be particularly suited to cases in which the problem is solely that of terminating a paroxysm of auricular tachycardia]

There are several ways of applying digitalis in a case of auricular flutter. In many instances, there is little more to it than the fact that a normal rhythm appears after very large doses of digitalis have been given In others, however, the digitalis will convert the flutter into fibrillation, and the fibrillation may persist as long as the digitalis is continued In these, the restoration of a normal rhythm takes place only after the digitalis is discontinued Here also, a rapidly eliminated digitalis preparation is the most practical

Dr Smith Dr Pardee, could we have some remarks from you on the subject of heart block and the Adams Stokes attacks?

Dr Pardee In patients subject to Adams Stokes attacks, the diagnosis of the particular mechanism is very important The mechanism is often one of prolonged A V conduction in which there is a fleeting period of complete dissociation This gives rise to spells of transient giddiness, usually without convulsions because the normal conduction soon reappears

Among patients who have complete heart block and who develop more severe attacks of syncope, there are 2 mechanisms In one type, the syncope is due to ventricular arrest These patients usually have an irregular ventricular rhythm with a slow rate of 20 or so In the second type, the syncope

may be associated with ventricular fibrillation These patients may have a somewhat higher ventricular rate but the rhythm is apt to be interrupted by premature contractions Such a finding between the attacks should make one suspect that the convulsive seizures are probably due to ventricular fibrillation Digitalis and ephedrine to increase the rhythmicity of the myocardium are often helpful in the types of heart block in which the syncope is due to ventricular arrest, but they seem to aggravate the type in which ventricular fibrillation occurs Sedatives such as bromides or phenobarbital, seem to be helpful in the patients in whom convulsions occur as the result of ventricular fibrillation

At this point, it should be mentioned also that there is no contraindication to using digitalis in the patient with chronic heart block if heart failure is present

Dr Modell How would you treat congestive failure which might develop during a paroxysm of one of the ectopic rhythms? Assume that you had not yet found the proper drug or combination of drugs to abolish the paroxysm I should also like to know whether it is not true that the control of the failure sometimes abolishes the ectopic rhythm

Dr Smith Dr Deitrick will you try your hand at this?

Dr Deitrick If it happens to be a supraventricular tachycardia, it is fortunate because one can then use digitalis freely In the case of ventricular tachycardia, I do not have the courage to digitalize even in the presence of congestive failure I try to stop the paroxysm of tachycardia as quickly as possible

Dr Modell How about using a mercurial diuretic?

Dr Deitrick I would use it, but I do not think that is the answer to the problem One simply has to abolish the ectopic rhythm before the function of the heart can be materially improved

Dr Pardee I know of 2 patients with ventricular tachycardia in whom failure developed and was treated with digitalis Both of them died

Dr Smith Was quinidine used in these cases?

Dr Pardee Quinidine had been used but was ineffectual Everything we tried failed

Dr Smith I take it that the last thing you tried was digitalis

Dr Pardee Yes, the ventricular tachycardia was somewhat slowed by quinidine but it was not possible to abolish the rhythm When the patient developed frank signs of failure he was digitalized

Dr Gold I think Dr Modell s question merits more attention An intensive course of dehydration, by means of the use of milk as the sole diet, liberal water intake, and a daily intramuscular injection of 2 cc of a mercurial diuretic, should go a long way in helping to control the congestive failure which develops during a paroxysm of a rapid ectopic rhythm I am inclined to believe that these measures are more effective than digitalis in such cases, so that one does not need to worry too much over the fact that digitalis is omitted

There is an important point in his second question also Paroxysms of ectopic rhythm are sometimes the first manifestations of a failing heart There may be paroxysms of auricular fibrillation, *auricular tachycardia*, *ventricular tachycardia* and others An effective course of dehydration by means of salt restriction and frequent doses of the mercurial diuretic *sufficient to reduce the patient to his dry weight* is often successful in abolishing attacks of ectopic rhythm and preventing their recurrence

Dr Modell I was interested in the comment on the matter of having atropine on hand in the event that carotid sinus pressure caused cardiac asystole It is not quite clear to me what purpose it would serve, since if there is asystole, there is no circulation and even if the atropine were injected into the vein, or directly into a chamber of the heart there would be no means of transport to the site of its action I know that carotid pressure may produce cardiac standstill of duration that is very disquieting it may last long enough to give rise to

an asphyxial convulsion, but I believe it is a fact that escape from vagal control is the rule, and that disaster from the use of carotid pressure is extraordinarily rare, if indeed it occurs at all

Visitor I would like to ask Dr Gold what he does for a paroxysm of sinus tachycardia

Dr Gold This is the most common form of tachycardia, and we have no specific treatment for it

Dr Smith How about removing the cause?

Dr Gold That is what we try to do, but we cannot boast of our success I assume that we may omit from consideration the patient with Graves' disease or with fever in whom sinus tachycardia occurs The patients who complain of attacks of rapid heart action and in whom these turn out to be paroxysms of sinus tachycardia are individuals with autonomic imbalance, disturbed psychic states, tension states, and the instability of the menopause We have no drugs which act directly to produce persistent slowing of the sinus rhythm We try to treat the nervous state We sometimes use sedatives or suggestion, or whatever else seems indicated by the various and sundry problems presented by the particular individual They may improve, but, on the whole, the therapeutic results are not particularly striking

Dr Smith Are there any further questions?

Visitor Suppose you were faced with the problem of a patient who had just suffered a myocardial infarction which precipitated auricular fibrillation with a ventricular rate of 160 a minute What would you do? Would you try to abolish the fibrillation or merely to slow the ventricular rate?

Dr Smith Would you answer that, Dr Eggleston?

Dr Eggleston I have been confronted with that problem on several occasions I do not try to restore the normal rhythm Most often, the auricular fibrillation which occurs in association with an acute coronary thrombosis is of short duration It has been my practice to resort to digitalis to slow the ventricular rate and to relieve or prevent congestive failure I do

not believe there is any contraindication to the use of digitalis, even in fresh infarction

SUMMARY

Dr Gold The treatment of disorders of cardiac rhythm was explored in the conference this afternoon This was a very large undertaking There are several types of disorders of rhythm There are various devices for distinguishing one from another It is important to do so, for there are significant differences in the treatment of each, and the most successful results depend on the use of measures specifically suited to the particular problem A special conference could be profitably devoted to any one disorder of rhythm

There has been no attempt to exhaust the subject, but many points of practical interest have been brought out in the account of experience and opinion by the various participants Many of the details cannot be satisfactorily summarized without repeating the conference The following disorders of rhythm received attention premature contractions auricular and nodal tachycardia, auricular flutter, auricular fibrillation, ventricular tachycardia, and heart block There was some discussion of the management of congestive failure in the course of a paroxysm of abnormal rhythm, and the problem of ectopic rhythms occurring in the hyperthyroid state It was pointed out that three distinct problems prevail in cases of disordered rhythm, namely, that in which the disordered rhythm is a chronic phenomenon and is to be allowed to continue, that in which an acute paroxysm needs to be terminated, and that in which the problem is essentially one of preventing recurrences Means for differential diagnosis were described, namely, certain clinical features, the electrocardiogram, and carotid sinus pressure and various devices exerting similar effects

The application of several drugs was discussed in some detail, such as, quinidine, digitalis magnesium sulfate, procaine,

Mecholyl ipecac, ephedrine, morphine and other sedatives In a patient with a paroxysm of rapid heart action which does not appear to be damaging the circulation unduly, there are some who prefer to give a dose of morphine to make the patient more comfortable and let the problem rest until the abnormal rhythm ceases spontaneously Digitalis appears to be the drug of choice for the paroxysm of auricular and nodal tachycardia While Mecholyl is very effective, it is so apt to produce disturbing symptoms that it is best to keep it in reserve for use when other measures fail Quinidine is the standard remedy for an attack of ventricular tachycardia, and when for one reason or another it proves inadequate, an intravenous injection of magnesium sulfate is sometimes effective There are risks involved in the use of all these drugs to abolish a paroxysm of abnormal rhythm and technics were described for reducing the hazards to a minimum

Attention was called to the fact that there are many situations in which a differential diagnosis among the disorders of rhythm is difficult or impossible to make but that even under those conditions a specific form of therapy is still available, for quinidine is highly effective against 5 of the more common disorders of rhythm—premature contractions, paroxysmal auricular tachycardia auricular flutter, auricular fibrillation, and ventricular tachycardia Strong emphasis was placed however, on the desirability for making every effort to establish the precise mechanism before treatment is started, for only then is the most rational and effective plan of therapy possible

Finally, the point was made that one should always bear in mind the underlying state of the heart in which a rapid ectopic rhythm has suddenly appeared The abnormal rhythm is a dramatic event and may engage the attention of the examiner to the exclusion of other factors of far greater importance than the abnormal rhythm, such as Graves disease or an acute coronary thrombosis

Medical Management of Hypertension

Dr. Harry Gold: The treatment of hypertension by non-surgical means is the topic of the conference today. Dr. William Goldring of New York University College of Medicine, who has for many years pursued this subject as a clinician and investigator, will give us the benefit of some of his extensive observations and rich experience. Dr. Goldring will open the discussion.

Dr. William Goldring: The cause of hypertension is not known. There is no known cure. The management of the disease at the present time involves the use of measures that are essentially empirical. These fall into three categories on the basis of the objectives: to reduce the level of the blood pressure, to alleviate symptoms, and to eliminate one or another of the supposed causes. Claims for therapeutic value in essential hypertension have been advanced for large numbers and highly diversified agents and methods, such as sympathectomy, psychotherapy, salt-restricted diets, thiocyanate, and a host of others. Such a state of affairs in the therapy of any condition gives rise to the question whether any of the measures have any substantial utility. Under these circumstances, it becomes a matter of some importance to decide what objectives are worth pursuing. It is probable that no one would doubt the desirability of eliminating the cause, if the cause were known. There is also a legitimate place for measures which exert no other effect than to control distressing symptoms. But the position is not quite so clear in the matter of lowering the blood pressure. Opinion is sharply divided on

the question whether measures, the primary action of which is only that of lowering the blood pressure, have any substantial merit in the control of hypertensive disease Arteriolar disease is the factor which ultimately brings about disability and death in these cases, and to prevent or retard its development would clearly represent a sound therapeutic objective There are, however, no measures which are known to act directly to interrupt or reverse the process in the arterioles Attempts to approach this indirectly by lowering the blood pressure involve an assumption concerning a causal relation between high blood pressure and arteriolar disease In spite of all that has been said and written on this subject, the degree of dependence of vascular disease on the level of the blood pressure remains without sufficient proof There is no convincing proof that prolonged lowering of the blood pressure by means of sympathectomy or other measures reduces vascular accidents but it should be stated that there is also no proof that it fails to protect the vessels against such accidents With our knowledge being what it is at the present time, measures designed to lower the blood pressure may be viewed as experiments worthy of pursuit and further study

Sodium thiocyanate has achieved some prominence for the purpose of lowering the blood pressure in hypertensive disease After a preliminary wave of enthusiasm for this drug, interest in it waned, presumably by reason of a high incidence of toxic effects The use of the drug was revived by the suggestion that repeated determinations of the concentration of thiocyanate in the blood would prevent overdosage, and that toxic effects would be infrequent if the concentration were maintained at levels between 6 and 12 mg per cent Dr Chasis and I re examined the problem of thiocyanate in a group of hypertensive patients Instead of measuring the blood level we determined the amount excreted daily in the urine which, when subtracted from the daily dose, yielded information regarding the daily retention in the body We did not escape

diastolic pressures declined to lower levels and remained there for 12 to 24 hours Such a reaction differs in no way from that following the parenteral injection of other foreign proteins such as triple typhoid vaccine The administration of tyrosinase inactivated by heat produces a comparable decline of the blood pressure, a fact which suggests that the fall of the blood pressure after tyrosinase is not the result of a specific antipressor agent, but of a nonspecific protein material Vitamin A has been found to increase renal blood flow, filtration rate, and maximal tubular excretory capacity in hypertensive patients *Several investigators have administered Vitamin A* orally in doses as much as 400,000 International Units a day for periods of 3 months but, in spite of these changes in the kidney, no significant effect on the blood pressure has been observed I believe that *experimental and human hypertension* are not alike, and that treatment of human hypertension based on the assumption that they are similar is ineffective

Finally, there is the therapy designed to alleviate distressing symptoms without regard to the level of the blood pressure For this purpose, I know of no more potent measure than psychotherapy By this term I do not refer to any particular technic Many of these patients are obsessed with fear and anxiety in the knowledge that they have high blood pressure Any method which succeeds in assuring them that not all patients with high blood pressure are alike and that if they have it they do not necessarily stand on the brink of disaster is often successful in allaying their fears and anxiety and is apt to go a long way in *controlling the most unpleasant discomforts* It is sometimes astonishing to note the extent of rehabilitation that is possible by simple psychologic p

This approach to the problem ... pertensive does not influence the course of ... e At the time *hypertension is not* curabl ... r the rar pheochro ... a and the ver ... ce of u

renal disease I have discussed only the matter as to how to eliminate certain clinical manifestations of hypertensive disease the subjective symptoms and the lowering of the blood pressure I believe that when both of these can be accomplished there still remains the danger that the patient and doctor are lulled into a false sense of security, for it is extremely doubtful whether either of these measures or any others available at the present time actually retard the progress of the hypertensive disease The attitude which I have expressed toward the present-day treatment for hypertension is pessimistic indeed but I am fully convinced that it represents the true state of the current therapy I also believe that we are more apt to achieve a solution of the problem by facing these facts squarely than by concealing them behind a mass of therapies for the value of which no satisfactory evidence exists at the present time

Dr Gold You have heard how Dr Goldring views the treatment of hypertension Are there any in the audience who think differently about it? I am sure that Dr Goldring is willing to try his hand at any reasonable questions which will come his way

Dr Harold Stewart I would agree with some of the points made by Dr Goldring I should like to ask him, however, what he does with a patient with hypertension who consults him What does he tell that patient?

Dr Gold I have on my card precisely the same question What do you tell the patient with hypertension who comes to your office for advice? Dr Goldring would you like to take up that point at this time?

Dr Goldring I think there is apt to be no disagreement as to what to tell the hypertensive patient whose complaints are due to the complications of hypertension cardiac and cerebral These are fairly clear-cut Perhaps it is not necessary to consider these aspects for there is likely to be no important differ

ence in our approach to these phases of the therapeutic problem I assume that your question relates to the hypertensive patient who consults us for advice, but who has no disability related to specific organs It is in relation to the treatment of such patients that the attitude of the doctor counts for so much If the doctor believes he has means for eliminating renal ischemia and he treats the patient with one or another kidney extract, or assures the patient that one or another operation to increase the blood flow in the kidney is likely to bring about a cure, I am quite confident that he is on the wrong track and that the patient has nothing but disappointment in store for him If the physician believes that lowering the blood pressure is an important objective, he may prescribe thiocyanate, nitrites, sedatives, or other agents intended to produce the same effects In this case I also think that the physician is on a track unworthy of his efforts

You asked me what I would do for the patient with hypertension who consults me Clearly, what I would do would depend on what kind of problem the patient presents My treatment would, in all probability, not differ materially from that of anyone else if the patient presented cardiac or cerebral complications I would not prescribe measures for the purpose of eliminating renal ischemia, since I believe that such measures as are available are ineffectual Also, I would not prescribe any measures for the supposed purpose of lowering the blood pressure, for, as I have indicated, these are also without evidence of benefit If the patient is apprehensive, if his knowledge of having high blood pressure interferes with his capacity to carry on I would do what I can to reassure him that matters are not as bad as he thinks they are in the hope of restoring his confidence I have applied the term 'psychotherapy' to this treatment I should emphasize that I do not have in mind the detailed methods of the psychiatrist Sympathetic understanding and reassurance accomplish amazing results

Visitor If there are no special symptoms do you prescribe any medication?

Dr Goldring Sometimes I do and sometimes I do not It all depends on what I judge to be necessary in the particular individual to establish confidence that his elevated blood pressure is not as serious as he believes it to be and that in spite of his blood pressure trouble a long and useful life is in store for him

Dr Walter Modell What does Dr Goldring think of the value of sympatholytic drugs such as tetraethyl ammonium or dibenamine?

Dr Goldring These agents have been disappointing Their early promise to produce persistent lowering of the blood pressure has not materialized I believe they have no practical place in the management of hypertensive disease

Dr Gold Do you ever put these patients to bed?

Dr Goldring Bed rest is useful for an impending crisis It is often valuable for the patient with repeated anginal seizures on the slightest effort and in those with signs of serious encephalopathy Otherwise I see no benefit to be derived from confinement to bed I do not put patients to bed simply because their blood pressure is high

Dr McKeen Cattell Since vascular accidents are apt to occur in association with high blood pressure I should like to ask Dr Goldring whether he would not concede some value in a treatment that lowers the blood pressure

Dr Goldring Perhaps that is where our points of view differ I am not convinced that the level of the blood pressure has anything to do with the occurrence of cerebral accidents It is my opinion that cerebral accidents which occur in hypertensive disease are the result of the vascular disease itself but, as I have already indicated there is not yet sufficient evidence to decide the question and the possibility that high blood pressure may predispose to cerebral accidents remains unsettled

Dr. Gold: We have not heard from you on these matters, Dr. Pardee. What are your views on the points which have been raised?

Dr. Harold E. B. Pardee: I hesitate to express my views since they cannot be supported by scientific evidence which meets the highest standards. Nevertheless, I have some opinions about them which are in my belief without reasonable doubt. I believe that the persistent high blood pressure produces intimal changes in the arterioles and perhaps the larger vessels, with thickening and weakening of the wall of the vessels. I am in agreement with others in these views, and so I believe that any measures which will reduce the level of the blood pressure for any appreciable time should prove useful in the management of hypertensive disease. By the use of thiocyanate, some of my patients have maintained a systolic pressure of about 30 mm. lower and a diastolic pressure of about 20 mm. lower than would otherwise have been the case. These effects maintained over a number of years seem to me to have yielded favorable experience. I have encountered some toxic results, but no fatalities.

I agree with Dr. Goldring on the importance of anxiety in hypertensive patients. They are often greatly relieved by interviews which allay their fears and establish confidence in the position that their hypertensive trouble is not necessarily a disastrous disease. It is my observation, however, that these very measures serve not only to control the apprehension but also to lower the blood pressure, and in that way also to retard the development of the hypertensive disease itself. There is in the daily life of everyone experience which tends to cause temporary increase in the blood pressure. Believing as I do, that an elevated blood pressure is harmful, I pursue the plan of discussing with patients ways and means for avoiding extremes of physical effort and exposure to emotional stress and strain, such as are often encountered in both play and work.

I now refer only to patients with hypertensive disease in the early stages. I have no doubt that the treatment of patients with arterial and hypertensive disease in the advanced stages would not differ materially in the hands of Dr. Goldring or myself.

Just a word about the use of phenobarbital. I believe it is often more than psychotherapy. I have the impression that it often exerts beneficial effects through direct lowering of the blood pressure and producing similar results by its action in allaying nervous tension and emotional turmoil.

Dr. Gold: Dr. Pardee, I should like to ask you the same question: Do you ever put these patients to bed?

Dr. Pardee: Yes, I sometimes do. I put to bed the same kind of patients who are treated in a similar manner by Dr. Goldring, namely, those with serious cardiac symptoms and those with serious cerebral symptoms. I go a bit further, however, for I sometimes put to bed patients who have given indication that prolonged rest will produce substantial lowering of the blood pressure. I do this because I believe that lowering of the blood pressure is in itself an important measure in patients with hypertensive disease. I should state that by the term "prolonged" bed rest, I do not refer to a few days or a week. I have in mind much longer periods than that as effective in bringing the pressures down to significantly lower levels.

Dr. Gold: Are there any other questions?

Visitor: May we have an expression of view on the point whether it is wise to let patients know the level of their blood pressure? Is it advisable to tell them just what it is or to keep them in the dark about it?

Dr. Goldring: There is no fixed rule about that. Some patients are better off when they know the level of their blood pressure. Others are better off when they are kept completely in the dark about it.

Dr Pardee How would Dr Goldring prescribe alcohol? Would it be a medication to be taken a fixed number of times daily? What would be the dose, and why?

Dr Goldring I can answer all the questions except the "why" I prescribe it as I do any medication The amount depends on the patient s tolerance Some can tolerate no more than a thimbleful 3 times daily, others seem to show no limit The amount required is that which will produce a more or less continuous state of vasodilation throughout the day

Dr Gold I would have suspected that, if Dr Goldring would favor alcohol, he would do so by reason of its action in controlling emotional tension rather than by reason of its vasodilator action which might lower blood pressure, since he holds in so low esteem the reduction of blood pressure in the treatment of hypertensive disease It may well be, however, that the cerebral effect of alcohol is partly due to a vasodilator action

Dr Goldring has clearly stated the principles he pursues in the treatment of hypertensive disease I wonder if we might come somewhat closer to the details by the account of a specific case Consider, if you will, a 47 year old man who discovered he had hypertension at the age of 45 In the 2 years that have elapsed, the blood pressure has varied considerably in the range of 230 to 280 systolic and 130 to 140 diastolic, the diastolic having reached as high as 180 on two or three occasions He has continued fairly active in business He has developed troublesome headaches, a few retinal hemorrhages moderate enlargement of the heart and the electrocardiogram has developed a negative T wave in lead 1 and 2 On the advice of his family physician he has had several periods of complete bed rest at home, each for 2 or 3 weeks He has had abundant reassuring advice and he has so adjusted his responsibilities in his business as to curtail both physical and emotional stress to a very considerable degree There was no improvement in terms of his symptoms and signs, and before long surgical

sympathectomy was advised. How would you have tackled that problem?

Dr. Goldring: Is that question for me?

Dr. Gold: Yes, I should like to know what specifically you would do, assuming that you did not favor sympathectomy.

Dr. Goldring: I would try to find out why the patient was disabled, what particular symptom or state of mind was in need of attention, and I would do what I could to correct it. There is nothing that I know, however, even sympathectomy, that would halt the progress of the disease which has reached that point.

Dr. Modell: Would you say something about the use of dehydration in that kind of patient?

Dr. Gold: I am glad to have the opportunity to discuss dehydration as a measure in the treatment of hypertension. Dr. Goldring has already alluded to simple salt restriction and the so-called rice diet in the treatment of hypertension. There are some recent publications which support the position that salt restriction lowers the pressure in hypertensive patients. During the use of dehydrating measures against congestive failure which had developed in hypertensive patients, I was struck by the fact that in many the blood pressure declined to levels that were normal or almost so. They were levels much below those which prevailed long before any suspicion of congestive failure. These observations suggested the desirability of a trial of dehydration in essential hypertension. Our experience up to the present time leaves us with no doubt that a regimen of dehydration, such as we employ in congestive failure, produces favorable results in hypertensive patients who present no symptoms or signs of congestive failure. The proportion of hypertensive patients who show a conspicuous response is not large, and as yet we have discovered no means for sifting out in advance those who are likely to respond.

The patient whose history I have just described was sub-

Dr Goldring My first objection to the notion that these instances indicate dehydration to be a valuable measure in the treatment of hypertension is the fact that the blood pressure level was the sole criterion

Dr Gold But in the one, fairly severe headaches subsided, and in the other, shortness of breath

Dr Goldring However, symptoms are so susceptible to all kinds of treatment, that their disappearance cannot be used as an index of a specific action The regimen you described could only lead to sodium and water depletion Sodium depletion by restricting the diet produces no such effects on the blood pressure, water depletion by mercurial diuretics is only a temporary expedient and could not account for the prolonged effects I would therefore be inclined to regard it as another form of psychotherapy

Dr Gold I should state that I do not pretend to know what factors in this regimen account for the results There is rest in bed, loss of body weight, salt and water depletion, a daily injection of the mercurial, and a systematic plan of treatment with all the abundance of psychologic content found in any systematic program of therapy Psychic influences are conveyed by any and all of these factors However, the fact that the blood pressure showed a marked decline, that the electrocardiogram returned to normal that severe headaches subsided, and that these changes persisted during the year and a half of treatment, makes it difficult to assign the results to the psychic effect of the treatment alone

Dr Pardee Was there any evidence of heart failure in these patients in the form of diminished vital capacity or increased venous pressure?

Dr Gold Neither vital capacity nor venous pressures were determined The elderly woman with a gallop rhythm and shortness of breath may well have had heart failure although there were none of the classical signs, no pulmonary rales, no enlargement of the liver, and no edema of the extremities

jected to this treatment He was placed at complete bed rest in the hospital His diet was restricted to 6 glasses of milk daily, representing 1 5 Gm of salt, and he received 6 glasses of water daily He also received a daily intramuscular injection of 2 cc of Mercuhydrin Within 2 weeks a radical change was in evidence He lost 6 pounds of body weight and remained at the new level, the blood pressure declined to a level of about $^{180}/_{100}$, the headaches subsided and the negative T waves in lead 1 and 2 returned to positive T waves After 6 weeks he was discharged from the hospital and continued the regimen at home in a modified form and with gradual lifting of restrictions during the ensuing 12 months before return to work, progressive increase in activities from complete bed rest to being up and about the major part of the day, liberal diet with salt restricted to approximately 2 Gm daily, 2 cc of Mercuhydrin once a week He returned to work and, 18 months after the hospital experience, his condition was still essentially similar to that on the day of discharge from the hospital

This was the case of a fairly young man with advanced but uncomplicated hypertensive disease I have here the account of a somewhat different case, an obese woman, 66 years of age, with a 10 year history of hypertension, with a blood pressure around $^{260}/_{110}$ during recent months of observation as an ambulant patient She had a markedly enlarged heart gallop rhythm, and some shortness of breath Various doctors whom she consulted had advised surgical sympathectomy She was also placed at complete bed rest in the hospital on a dehydrating regimen similar to the one I just described Her body weight leveled off after a loss of 20 pounds and the systolic blood pressure after a decline to approximately $^{160}/_{90}$ The gains were still there several months after discharge from the hospital

Dr Goldring do you have any experiences of this kind with rest and dehydration? Have you any opinion about it?

sclerotic and hypertensive heart disease followed by failure rather than failure resulting in elevated blood pressure.

Dr. Stewart: I note that in the first case the treatment involved a restriction of salt to only about 2 Gm. a day, and there was the use of the mercurial diuretic which would tend to pull out salt. I would attribute the effects in that case to salt privation since the changes are those which one would expect in patients who show some response to low salt.

Dr. Gold: I agree with that. Shall I then assume that you also regard dehydration as a satisfactory measure for the treatment of some cases of hypertension?

Dr. Stewart: No, I do not believe in dehydrating patients. I believe in keeping them free of any excess fluids they may have, but when dehydration is produced, the result is carried to the pathologic side.

Dr. Gold: Time is so short that I am eager to avoid what may seem to be merely a play on words. However, since the matter is raised, it might be worth pointing out that the term dehydrate is a useful device in the English language for expressing in the broadest sense the notion of the loss of water. When the term is used in relation to a particular entity, a special definition is required to avoid confusion, such as the removal of the constitutional water from a salt given in Gould's *Medical Dictionary*, a pathologic state of excessive fluid loss characterized by a particular group of symptoms and signs, or a form of treatment of congestive failure in which the optimum amount of extracellular fluid is allowed to remain.

Visitor: I wonder whether Dr. Goldring is acquainted with any studies which relate the blood volume to the blood pressure?

Dr. Goldring: There have been many studies on blood volume, blood viscosity, and cardiac output, but in no instance, as far as I know, has a relationship been found between these factors and the level of the blood pressure.

Visitor: Do you prescribe any special diet for your hyper-

The man of 47, however, presented no signs or symptoms of a failing heart

Dr Goldring Would you be willing to admit that a chart similar to the one you described could be drawn from the files of a long term follow up clinic with patients who have had no dehydration treatment?

Dr Gold I suppose one could, but I believe that the number which would present the essentials of the case I described would be very small There are many cases of hypertension with spontaneous remission But you will recall that the case I described was that of a relatively young man with a very high blood pressure, retinal hemorrhages, and severe headaches, whose condition was growing progressively worse, who showed no improvement during several periods of bed rest and whose resistance to treatment led to the recommendation of surgical sympathectomy It was in a person with that history in whom prompt improvement appeared during bed rest and dehydration I have a notion that histories of that kind will not be easy to find among patients who have not been subjected to the regimen of dehydration

Dr Stewart Many years ago Dr Alfred Cohen pointed out that, in some patients who develop heart failure, the blood pressure rises while in others it falls, and that with recovery the pressure tends to return to its normal level The second patient who had shortness of breath and a gallop rhythm, who improved with hospitalization and a diuretic regimen, would have to be eliminated as a case of lowering of the blood pressure as the specific result of dehydration

Dr Gold The point which Dr Stewart made regarding Dr Cohen's observation on the relation between heart failure and change in blood pressure is sound, and has been amply confirmed However, it might be well to mention the fact that this person is a patient of a member of our staff who discovered she had hypertension about 10 years ago, long before any complaints suggesting heart failure It is therefore a case of arterio-

sclerotic and hypertensive heart disease followed by failure rather than failure resulting in elevated blood pressure

Dr Stewart I note that in the first case the treatment involved a restriction of salt to only about 2 Gm a day, and there was the use of the mercurial diuretic which would tend to pull out salt I would attribute the effects in that case to salt privation since the changes are those which one would expect in patients who show some response to low salt

Dr Gold I agree with that Shall I then assume that you also regard dehydration as a satisfactory measure for the treatment of some cases of hypertension?

Dr Stewart No, I do not believe in dehydrating patients I believe in keeping them free of any excess fluids they may have, but when dehydration is produced, the result is carried to the pathologic side

Dr Gold Time is so short that I am eager to avoid what may seem to be merely a play on words However, since the matter is raised, it might be worth pointing out that the term dehydrate is a useful device in the English language for expressing in the broadest sense the notion of the loss of water When the term is used in relation to a particular entity, a special definition is required to avoid confusion, such as the removal of the constitutional water from a salt given in Gould s *Medical Dictionary*, a pathologic state of excessive fluid loss characterized by a particular group of symptoms and signs or a form of treatment of congestive failure in which the optimum amount of extracellular fluid is allowed to remain

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Dr Goldring There have been many studies on blood volume blood viscosity, and cardiac output but in no instance, as far as I know, has a relationship been found between these factors and the level of the blood pressure

Visitor Do you prescribe any special diet for your hyper

tensive patients? I have in mind especially protein and fat restriction

Dr Goldring I do not think there is any point in restricting the diet in any way for the purpose of reducing blood pressure I not only allow a patient to eat as much meat as *he wants, but I urge him to do so Until* we know more about this disease, its treatment will have to consist of treating the patient, and not only the symptom—the hypertension I think it is there that most of the treatments at the present time bog down, the patient is disregarded and a symptom is treated The consequences are either no effects at all or effects that are unpleasant

Dr Gold Our time is about up

SUMMARY

Dr Gold A large proportion of the measures which have received attention for the treatment of hypertension in recent years were discussed in the conference this afternoon There were phenobarbital, thiocyanate, the rice diet, salt restriction, weight loss, renal extracts, tyrosinase, the diet limited in protein and fat, vitamin A, vitamin C, rutin, tobacco, alcohol, *tetraethyl ammonium dibenamine, bed rest, and* a regimen of dehydration One of the speakers with an extensive clinical and scientific experience in this field elaborated his belief that nearly all of these measures not only are without value, but promote, by their use, the failure to face squarely the limitations of our knowledge, thereby retarding scientific investigation He was inclined to discourage smoking but regarded alcohol with some favor He stressed the points that the high blood pressure in so-called essential hypertension is only one of the many manifestations of hypertensive disease and not the disease itself, that the cause of the disease is not yet known, that the basic factor which *ultimately leads to* disaster is arteriolar degeneration, and that the persistent efforts to lower the blood pressure as a primary therapeutic

measure is without satisfactory evidence as a means for retarding the progress of the arteriolar trouble or protecting against vascular accidents He expressed his position without compromise that psychotherapy is the most effective assurance against disability in the hypertensive patient Although the value of the control of physical and emotional stress is quite generally appreciated views concerning treatment in other respects differed widely and in these contrary opinions were voiced with similar conviction There was the point that the current medical treatment of hypertension represents much more than psychotherapy that the mere lowering of the pressure by a drug such for example as thiocyanate not merely enhances the sense of well being through reassurance and allaying anxiety but by removing physical stress on the heart it retards its enlargement with its consequent tendency to failure and slows the process of arteriolar degeneration reducing the hazard of vascular accidents Also experiences were cited favoring the view that a regimen of dehydration with a milk and water diet and the mercurial diuretic given in frequent intramuscular injections a program similar to that employed in congestive failure produces in some hypertensive patients free of congestive failure striking and protracted results indicative of essential improvement represented by such changes as loss of weight very large decline of the level of the systolic and diastolic pressure subsidence of severe headaches cessation of the repetition of fundal hemorrhages and change of the negative T_1 and 2 to positive T_1 and 2 in the electrocardiogram These observations also failed to pass without vigorous disagreement

It is fortunate that this conference is intended for the profession and is not likely to reach any considerable number of nonmedical readers For the victim of hypertension or for the prospective one it can hardly be considered a source of encouragement There is also the fact that the patients receiving predominantly psychotherapy are apt to lose a fair share of

their response when the precise nature of the treatment becomes known to them.

The results of this conference point sharply to what is wanting. It is clearly neither more pessimism nor more optimism regarding the treatment of hypertension, but more facts. These should be fairly easy to secure from investigations so designed as to yield statistically valid answers. For the present, it might even suffice to confine such studies to the drugs and measures mentioned in this conference for, concerning these, the discussion revealed little more than impressions and opinions.

Treatment of Painful Disorders of Skeletal Muscle

Dr Walter Modell The conference today deals with the treatment of painful disorders of skeletal muscle That pain of this sort presents a therapeutic challenge is demonstrated by the length of the list of measures used in treating it. Here is a list compiled by Dr Travell.

1 Psychotherapy
2 Heat, massage, baths, electrotherapy
3 Deep x ray therapy
4 Active and passive exercises
5 Supports, braces
6 Manipulation
7 Surgical section of muscle (e g , scalenus anticus)
8 Curare
9 Neostigmine (Prostigmine)
10 Quinine
11 Ammonium chloride
12 Vitamin E
13 Nicotinic acid
14 Analgesics salicylates morphine, codeine
15 Intravenous procaine
16 General anesthesia
17 Regional nerve block
18 Local block of trigger areas infiltration, needling, ethyl chloride spray

Dr Travell will open the discussion

Dr Janet Travell I shall confine my remarks to a special group of patients These are patients whose activities are limited by pain That is the complaint which brings them to the physician The pain is usually accompanied by restricted motion of one or more joints The limitation may be gross or it may only be discovered by carefully testing the range of motion of special muscle groups Occasionally, limitation of motion cannot be demonstrated Localized areas of deep tenderness are always present in one or more of the muscles about the joints which exhibit limitation of motion, but signs of acute inflammation, such as redness, heat, and swelling are lacking A change in contour due to spasm of a muscle or portion of a muscle is occasionally mistaken for swelling due to tissue exudate, but this does not happen often Some of these patients are confined to the house or bedridden, but the majority of them are only partially disabled and are working under serious handicaps Thus most of them are ambulatory, and they make up a large per cent of the patients who come to the office of the general practitioner or to the outpatient department of the hospital

There need be and often is no demonstrable organic disease The syndromes under discussion are usually referred to by such terms as stiff neck, painful or frozen shoulder, *tennis elbow, lumbago, sciatica* and *painful knees,* terms which do not imply any special etiology Of course, there has to be a cause One difficulty in the way of establishing the etiology is the fact that these disorders seem usually to be due to a combination of factors

Among the manifest causes the foremost is probably trauma The role played by trauma is obvious in the muscular spasm associated with joint sprains fractures, or contusions, but the role of trauma may be equally important even when the injury is slight or of such a nature that its connection with the pain syndrome *is not readily traced* The relationship is often overlooked because spasm is apt to develop gradually

after minor injury, and thus may not become really painful until even a few days later This applies not only to the effects of a sudden wrench or jerk noted at the time, but also to the muscular pain and stiffness which may follow an unusual kind of exercise or excessive exercise

Less frequently recognized and equally important as a cause of pain is chronic muscular strain In this connection we must recognize that hurry with its inefficiency of muscular movements, as in writing or ordinary household duties, places an increased load on the muscles Just as it takes more gasoline to drive a car a given distance at 60 miles per hour than at 30 miles per hour, there are speeds of muscular performance for optimal efficiency, and, beyond these, conditions of hurry at work create in effect a form of muscle strain

Another precipitating factor in muscular pain is chilling the body as a whole or cooling a specific area This effect is apparently achieved not only when the thinly dressed person stands in a biting winter wind but also on a hot summer day when the perspiring golfer sits in a gentle breeze under a shady tree on the nineteenth hole of the golf course Pain is apparently more apt to result from chilling when a person is fatigued Bierman inserted electrodes directly into the voluntary muscles and found that cooling the skin by a current of air resulted in a prompt fall of muscle temperature, presumably due to reflex vasoconstriction, and it may well be that this vasoconstriction plays a part in producing the pain

Visceral disease is an important cause of painful spasm of the voluntary muscles There are familiar examples of such visceromotor reflexes, for instance, the localized muscular spasm or abdominal rigidity which accompanies acute appendicitis, or any other variety of the acute surgical abdomen Another example is the splinting of the chest muscle in acute myocardial infarction It is not well known, however, that visceral disease may lead to persistence of pain patterns established during the acute attack and, furthermore, that this in

tractable pain sequel may be amenable to local block of trigger areas located in the spastic skeletal muscles

The etiologic factors in painful muscle spasm also in clude certain neurogenic causes I have in mind particularly nerve root irritation due to pressure, for example, by a herniated intervertebral disc The painful cramps of peri pheral neuritis, as noted in vitamin B deficiency, should be mentioned *Other precipitating factors include the toxins* of acute and chronic infections, tetanus, for example Cer tain metabolic factors may play a role in the development of spasm A high proportion of patients with such chronic muscular pain have low basal metabolic rates of the order of —15 to 20 per cent A few show a slight anemia, with 65 to 75 per cent hemoglobin In other patients, psychogenic factors seem to play a predominating role in the etiology of painful musclar spasm When any of these factors is pres ent, pain may be only temporarily relieved or may remain quite refractory to local treatment of the affected muscles un til the basic disorder is corrected This applies also to trauma induced by continuing or repeated muscular strain, but not to a single episode of trauma after which the results of local block may appear truly miraculous

I have been asked to discuss certain therapeutic measures directed at the muscle itself, namely, local infiltration of the intramuscular trigger areas and the application of ethyl chloride spray to the overlying skin We may group these procedures under the term, ' local block" therapy, in contrast to "regional nerve block "

The theory underlying this kind of treatment is that the painful spasm is an expression of a reflex which, once initi ated, is self propagating Thus, spasm leads to pain, pain to further splinting and spasm, and so the vicious cycle sustains itself Brief interruption of this pain cycle at any point may abolish it permanently, provided the conditions which initi ated it in the first place are no longer intact

To apply local block methods successfully, one should have a knowledge of the pain reference patterns of the different muscles of the body It is not widely known that each muscle gives rise to a specific distribution or pattern of referred pain which is relatively constant from person to person These patterns are not strictly segmental in distribution and they do not follow any peripheral nerve distribution Once these patterns have been learned, the source of pain can be readily predicted The site of origin of the referred pain is commonly spoken of as a "trigger area" When one is infiltrating the muscle, it is this area which must be hit directly with the needle

The presence of a trigger area within a muscle is demonstrated by the fact that when pressure is exerted on it, or a needle inserted into it (which also exerts pressure), a spread of pain is clearly perceived by the patient in its specific reference zone In other words, that spot is positively identified as the source of the pain felt at a distance The reference zone, which can be mapped in this way by mechanical stimulation of the trigger area, should coincide with the region where the patient complains of spontaneous pain If it does match, one may be sure that at least one of the sources of pain has been found

LOCAL INFILTRATION For local infiltration, we prefer a 0 25 to 0 5 per cent solution of procaine hydrochloride in physiologic saline There is no epinephrine in the solution It must be pyrogen free since the injection of pyrogens into these hypersensitive areas sets up intense after pain for as long as several days Obviously, care must be taken to ensure asepsis The skin is cleaned with alcohol and painted with mild tincture of iodine On routine testing a small proportion of ampoules have been found to be cracked or defective at the tip, and therefore all ampoules are boiled with the syringes and needles just prior to use Some of the details of the local infiltration technic were presented at a previous

therapy conference,* and we have not changed them in any important respect since The kind of material used for infiltration is not nearly so important as the place where it is put, provided of course, that the material is not toxic Trigger areas can be blocked by *infiltration with physiologic* saline or merely by needling the area, with no fluid injected Thus our observations confirm the benefits derived by the old Chinese technic of acupuncture Local infiltration or dry needling may be regarded as satisfactory when the procedure immediately abolishes local tenderness at the site of the trigger area, does away with the spread of pain induced by pressure, reduces the total quantity of spontaneous pain and obtains an increase in the range of motion if limited It should be noted that the use of procaine makes the treatment much *less* disagreeable to the patient *in that it cuts* down the intensity and duration of the pain reference set off by insertion of the needle We have as yet no satisfactory data as to whether the addition of procaine increases the efficacy of treatment as compared with physiologic saline alone So far, we have not learned how to reproduce experimentally the abnormal state known as a trigger area

At the first treatment, it is usually wise not to inject many different muscles, but to select one or two major trigger areas and obliterate them completely, by repeated infiltrations if necessary *This is important since incomplete blocking* of trigger areas is one of the causes of increased pain following injection At the next visit, an evaluation is made of the results of the first treatment A satisfactory response to local block therapy may be predicted at this time (1) if there was marked amelioration of pain after the treatment, even though this lasted for only a few hours (2) if the gain in motion which was noted immediately after injection has not been lost to any appreciable extent and (3) if the activity of the treated trigger areas has been reduced, as indicated by a

* *New York State J Med* 45:2095 (Oct. 1) 1945

change in the intensity of the pain reference induced by pressure and needling. If no appreciable benefit according to these criteria is noted after 2 or 3 treatments, it is considered not worthwhile to pursue this method further. In fact, if substantial relief is not secured rapidly, the patient will usually not submit to any more injections, since the momentary pain set off by needling trigger areas of high spontaneous activity may be very intense. An early appraisal of the results is, therefore, important.

In acute cases, one treatment is sometimes sufficient to secure complete and permanent relief. In long-standing cases, however, it seems that one muscle after another becomes involved in the process so that a multitude of trigger areas develop, and a series of treatments are usually required to eradicate all of these foci of pain. The second treatment is usually timed from 3 to 5 days after the first, and subsequent treatments are given at intervals of a week or two, as indicated.

ETHYL CHLORIDE SPRAY. The use of ethyl chloride spray was described for treatment of ankle sprains by Cozen and Hollombe in 1940, and as "surface anesthesia for the relief of painful motion" by Kraus in 1941. We have likewise found that this procedure may at times relieve pain and limited motion associated with muscular spasm, and in a manner that is sometimes remarkable. The application of the spray is so simple that we are apt to try it as the first procedure in most cases. The benefit to be derived from ethyl chloride spray can usually be estimated at once. A particular trigger area is selected and its sensitivity to pressure is noted; the overlying skin is then lightly sprayed during a period not exceeding 2 or 3 minutes, according to an interrupted technic which I shall describe, and the activity of the trigger area noted again. As in the case of local infiltration, a good response may be expected if the spraying immediately abolishes or reduces deep muscle tenderness and referred pain on pressure, increases the range

of motion, and reduces pain at rest or on motion If the effect of the spray as determined on one or more such test areas is not striking, we usually proceed at once to local infiltration with procaine If the effect of the spray is sufficiently encouraging, we may repeat this procedure at intervals as indicated, and an excellent result may be obtained by this method of treatment alone

We have found that attention to certain factors seems to increase the effectiveness of ethyl chloride spray, and we believe that the details are important The procedure, as we do it, is as follows The patient is made comfortable, and the part to be sprayed is well supported so that the muscles can relax The tube or bottle of ethyl chloride is held one to two feet away from the patient The spray is applied at an acute angle with the skin The stream is passed over the region of the trigger area in one direction, at a uniform speed with an even sweeping motion The motion is not unlike that used in applying paint to a wall with a brush The ethyl chloride on the skin is allowed to evaporate, and, about one second later, the sweep is repeated in the same direction This 'make and break spraying is continued with a regular rhythm Sometimes only one passage of the spray over a given trigger area will cause it to disappear, but more often it requires 15 or 20 such sweeps One may occasionally observe transient activation of the trigger mechanism by the spray If the spray is painful at first, or sets off referred pain when applied over the trigger area, the rest periods between sweeps are lengthened to allow the induced pain to subside In the intervals, that part of the body which is being sprayed is moved gently within the limits of pain to stretch the affected muscle

It should be noted that the nozzles of the ethyl chloride containers vary a good deal A commercial make should be selected which delivers neither too fine nor too coarse a spray A very fine mist seems to be relatively ineffective a

heavy stream spatters and is unpleasant to the patient, and also wastes the material

We are also using ethyl chloride spray as an adjunct to local infiltration of trigger areas, that is as soon as the in jections have been completed the treated areas are sprayed in the above manner This procedure seems to reduce the muscle soreness or lameness which ordinarily follows trauma due to needling and is in line with the observation that ethyl chloride spray may permanently relieve pain due to trauma, such as joint sprain

It seems scarcely necessary to mention that ethyl chloride is a highly volatile and inflammable liquid, so that fire haz ards must be eliminated It is also a general anesthetic agent, and care should be taken that the patient inhale as little of it as possible Since the vapor is heavy, the patient s head should be above the part sprayed Some movement of air in the room is desirable

The mechanism of action of ethyl chloride spray on trig ger areas in the muscles is probably different from that of the local infiltration and needling technics It is clear, however, that neither one depends on a local anesthetic effect in the ordinary sense of this term Neither can the effect of spray ing be due to refrigeration anesthesia of the structures be neath the skin Care is taken to avoid a degree of cold which produces aching or frosts the skin Furthermore it can be shown by the intradermal injection of an irritant solution that this method of light spraying which blocks trigger areas, does not block pain impulses even from the superficial layers of the skin

Adjuncts to Local Block I want to emphasize that local block is usually not the only therapeutic measure that we employ, because even in the apparently simple cases of acute spasm we are apt to find that something has been wrong with the muscles for some time before the acute attack We use, therefore, a system of treatment which combines a

variety of measures for the relief of painful muscle spasm

In the first place, we limit any form of exercise or work which places a heavy load on the affected muscles This is quite simply accomplished by telling the patient that he must avoid doing anything which produces pain which lasts for more than a second or two after the effort Pain itself is deleterious in that it reflexly builds up more spasm, therefore, it is unwise to attempt to drive a muscle beyond the point of pain Secondly, we direct the patient to move the part frequently in such a way as to provide gentle stretching of the affected muscles at regular intervals For instance if extension at the shoulder is limited, the patient may be directed to reach up and touch a marker on the wall every hour Stretching should be carried out within the limits of pain and never so forcibly as to produce a lasting ache after the stretch We rarely put the patient to bed, more often we get him out of bed

As soon as the acute pain is controlled by local block therapy, more vigorous exercises are instituted and it is determined by trial and error how much the patient can do That form of exercise is recommended which the patient formerly enjoyed and for which his muscles were previously trained and developed Swimming is often considered the best exercise to improve muscular function, but one cannot direct a person to swim who never learned how, and expect him to use poorly functioning muscles properly He may enjoy tennis, and, if so, his muscles will derive much more benefit from tennis than from another sport to which he was never accustomed or in which he was not skilled Furthermore, it is our experience that free moving and pleasurable games promote muscular relaxation to a much greater degree than does useful work about a house, such as painting carpentering and gardening, since these activities are all based on repetitive movements within a small range of motion

External heat is helpful, especially hot tub baths and hot

water bags Intense heat, such as diathermy, often seems to intensify the pain Massage is employed only when the intense pain has subsided, when trigger areas of high spontaneous activity are present, manipulation or massage of these areas may aggravate the pain On the other hand, when applied at the right stage, massage is very beneficial

We usually employ some internal medications Ascorbic acid is given routinely to every patient receiving local injection therapy, as a rule, 0 5 to 1 0 Gm by mouth daily In case of severe pain we use aspirin in doses up to 4 Gm daily This is occasionally combined with codeine We almost never prescribe morphine for obvious reasons Incidentally, the opiates are not nearly as effective in pain due to muscle spasm as they are in other forms of pain

An effort is made to discover mechanical factors which may have led to the evolution of the pain syndrome In particular, we try first to eliminate chronic strain associated with repetitive movements For instance if episodes of painful stiff neck recur in a certified public accountant who spends hours copying figures out of a book placed at his side, we have him place the book directly in front of him on a bookrest so that he can look up and down from the book to his paper without constantly turning his neck sideways Secondly, we try to eliminate hurry in the physical activities of the daily routine It is often possible to point out unessential items and timesaving devices but for this to carry weight the patient must be made to realize the necessity of reducing the daily burden on the muscles Finally, we often find it necessary to redesign the patient s furniture both at home and in the office, especially chairs in order to provide proper support for the framework of the body In cases in which the greater part of the waking hours are spent sitting seating facilities should be so designed that, as the muscles relax and the body tends to sag correct posture is maintained by the chair, muscle fatigue and joint strain are thus avoided Such

support cannot be adequately supplied by braces or corsets and we almost never use these latter devices

Dr Modell What do you visualize as taking place in the muscle that develops spasm?

Dr Travell Muscle spasm is an expression of a reflex mechanism which can be initiated and maintained either by local factors in a nearby area, or by distant factors as in visceral disease Spasm is characterized by shortening of the muscle, which cannot be relaxed voluntarily Neither can the muscle in spasm be passively stretched without pain It is tender to pressure Pressure usually causes a localized contraction in that portion of the muscle which is tender In ordinary use, such a muscle may appear to be weak If forcibly contracted, the spasm may be abruptly increased so that the muscle goes into what is called 'a cramp" If the spasm is very intense, it gives rise to constant pain at rest, and not merely to pain on motion

This description excludes other forms of muscle shortening, such as that observed in decerebrate rigidity, fibrosis, and contracture, which are not per se accompanied by pain, that is, pain on stretching the shortened muscle Also, in the latter conditions the muscles may not be tender to pressure

There is a good deal of confusion as to the precise meaning of the terms, spasm, spasticity, and rigidity I would like to hear Dr Wolff comment on this

Dr Harold G Wolff I am not sure that the difference between the shortening of decerebrate states and that of this reflex is understood, that is, why one is painful and the other is not All muscle shortening apparently is not painful There are certain patients whose muscles are in a state of over contraction for a long time without hurting Other people, however, do have pain There must be another factor besides shortening of the muscle, perhaps a circulatory derangement as well, or possibly the elaboration of a chemical agent which has threshold lowering properties

Dr Modell I would like to ask Dr Travell one more question Are all painful muscles in spasm?

Dr Travell I cannot answer that positively Probably not

Dr McKeen Cattell The normal postural reflexes, which we speak of as tonic activity of muscles involve a sequential activity of fibers The degree of pull is determined by the number of fibers which are active at any one moment, but normally no group of fibers stays contracted very long On the other hand, there might well be a more sustained contraction of a group of muscle fibers that would lead to a reduction in blood flow and pain due to ischemia

Dr Harry Gold Might not a large mass of fibers which remain contracted for a period of time create a pull between bundles and result in distortion of the muscle? Under these circumstances, the pull on the nerve fibers lying between contracted and relaxed muscle bundles might be a cause of pain

Dr Travell It is characteristic of these painful muscles which I see that the spasm is almost always more marked in some one part of the muscle than in another Thus, in the case of painful spasm of the pectoralis major in a thin person, it is easy to demonstrate that perhaps only one of the fan shaped sections of this muscle is exquisitely tender and persistently exhibits a localized contraction or twitch each time it is palpated, whereas the neighboring muscle bundles are not tender and do not exhibit this phenomenon of hyperreflexia This affords some basis for the idea that there may be an imbalance or distortion in the pull of different sections of muscle

Dr James Hardy Spasm of muscle means increased muscle tension, and I would like to ask Dr Travell whether she has been able to show an actual increase of tension in any muscle Does pain accompany such increased tension?

Dr Travell We have not made any direct measurements of muscle tension

graphic studies are usually made at this time to determine whether or not abnormal electrical activity of the muscles recurs If there is no such recurrence, intensive physical therapy is continued without curare

It should be of special interest to this group today that we see the pain controlled regularly by curare I think that since we started to use this drug, we have never had to give codeine or any other opiate, nor have we had to use sleep ing medication of any type Another symptom which is readily controlled by curare is constipation After curare, the acute poliomyelitic patient has practically no difficulty with evacuation, whereas those of you who are familiar with the nursing care of these patients know that constipation is often a real problem The cutaneous vasospasm of acute anterior poliomyelitis is also relieved by curare We have seen but 3 patients with cold extremities in about 120 cases that we have followed now for a period of two and one half years In those 3 patients, who developed cold extremities, one dose of curare a week has been sufficient to maintain normal skin temperature of the legs and arms Difficulty in swallowing in our bulbar cases is usually relieved within 40 minutes after the first dose of curare and this improvement is main tained Labored abdominal respiration in those patients who come in with what we call a *frozen chest* is relieved, and the spastic muscles are relaxed promptly by the action of curare so that these patients can breathe comfortably in an oxygen tent We have used a respirator in only 3 cases since we started to use curare Two of these patients died within 24 hours of their admission to the hospital Curare is not by any means a cure for acute anterior poliomyelitis It is merely an effective method of treating some of the symp toms

Dr Wolff May I ask Dr Ransohoff how he makes cer tain of the effectiveness of curare in poliomyelitis since he

uses both physiotherapy and curare? Has he another group which receive physiotherapy alone?

Dr Ransohoff The vagaries of the disease are so great that to ascertain differences in ultimate outcome due to curare, I would not know how to set up a control group However, our electromyographic studies show that physical therapy alone hot packs or stretching for instance does not accom plish the same results without curare as it does with curare Thus the therapeutic results are in a sense controlled by electromyography

Dr Wolff We have tried curare in a few patients with spastic states associated with myelitis to relieve spasm and indeed curare did relieve it but the patients were left so weak as the result of this action that it was of doubtful value I wonder whether the margin between relaxation of spastic muscles and weakness of the remaining useful muscles is wide enough for curare to be of any help in this problem

Dr Travell Differences in results may be due to differ ences in preparations In the chronic spastic states such as the cerebral palsies hemiplegias etc in which Schlesinger reported satisfactory results d tubocurarine in wax and oil was used exclusively He noted that with aqueous solutions of the curare alkaloids it was very difficult to secure the re laxing effect without unpleasant side effects

Dr Gold Dr Ransohoff would you recommend that a gen eral practitioner use curare or any of its preparations in his office for a patient with a sprained back or dislocated shoulder with a good deal of muscle spasm?

Dr Ransohoff The use of curare is not a satisfactory office procedure One has to be prepared to have the patient lie there for about 3 hours He won t be able to walk right away

Dr Gold What about a smaller dose?

Dr Ransohoff A smaller dose does not produce the desired effect With aqueous preparations of curare, it is apparently

sohoff's patients was mediated through a reduction in muscle spasm

Dr Modell Dr Hansson, how do you treat painful spasm of skeletal muscles?

Dr Kristian G Hansson In the painful spasm of acute anterior poliomyelitis, application of moist heat is our treatment of choice at the present time We prefer a therapeutic tank with a temperature of 106° F (41 2° C) for a half hour twice a day This procedure is followed by passive stretching to obtain the normal length of the muscles Another type of painful spasm occurs in connection with acute traumatic conditions, such as lumbosacral strains sprains, peritendonitis about the shoulder, and so forth In these conditions applications of heat, effleurage, manipulation, and stretching exercises are of benefit However, whatever therapeutic means are used to overcome the painful spasm, it is most important to follow it up by an attempt to restore the normal muscle length

Dr Travell Is it also your experience that in the extremely painful forms of muscle spasm the application of diathermy may sometimes produce an immediate exacerbation of pain?

Dr Hansson When painful muscle spasm is associated with an increased blood supply, as in the case of congestion the use of any form of heat, either external or internal, in the form of diathermy or short wave, is indeed often followed by an exacerbation of pain Under these circumstances the application of cold in the form of ice bags is more rational, and may be followed by relief of pain

Dr Modell Stretching a muscle in painful spasm sometimes relieves the pain and restores the normal range of motion, but then, at other times, stretching does harm Dr Liebolt, would you tell us something about this?

Dr Frederick Lee Liebolt The active or passive stretching of a muscle in spasm without anesthesia is effective in relieving pain and restoring motion in certain conditions for example, that which follows acute subacromial bursitis.

The act of stretching such muscles gives rise to pain during the procedure, but once the spasm is overcome, the pain disappears and the motion becomes normal Passive and active stretching of muscles which have shortened to the stage of contracture, as may be the case in fractures, bursitis, and trauma, is most important and will do no harm If the muscle is acutely inflamed, however, as in acute poliomyelitis, repeated active and passive stretchings will prove quite harmful, producing additional irritation and inflammation leading to fibrosis When the stage of fibrosis has been reached, stretching may do more harm than good The atrophied structures have been infiltrated or replaced by fibrous tissue, and here manipulation, without anesthesia will simply stretch this tissue and serve to stimulate additional fibroblastic activity, manipulation, under anesthesia, will tear the taut structures, produce hemorrhage, and simply traumatize the tissue further

Dr Modell How do you distinguish between spasm and contracture? What is the difference between spasm and spasticity?

Dr Liebolt Spasm is an involuntary muscular contraction which may be of short or long duration, but which is always temporary, contracture is an involuntary muscular contraction of long duration which, unless treated, is always permanent Although spasm and spasticity are sometimes used as synonymous terms I do not consider them to be the same, because spasm refers to a temporary, protective, and nonpathologic state of muscular contraction without changes in the reflexes while spasticity refers to a permanent, nonprotective, and pathologic state of muscular contraction associated with changes in the reflexes

Dr Modell Dr Wolff have you treated any patients with painful muscle spasm by psychotherapy?

Dr Wolff Muscles do contract as a part of a general state of tension and apprehension in which there is overalertness associated with quick movement and hurry in attempting to

stopped, the cramps recurred It isn t always effective and the largest tolerated doses may fail in cases that are indistinguish able from those in which it succeeds

Dr Wolff When I have used it, the side effects of the qui nine have been so disagreeable that the patients did not like it. In myotonia congenita, the patient prefers the moderate cramps to the effects of quinine I never tried it in the more painful states

Dr Modell What would you say about nicotinic acid?

Dr Gold For what purpose? For the histamine like, capillary dilator action to improve the circulation in muscle?

Dr. Travell Yes, I have used it in a few cases in fairly large amounts by mouth, up to a gram a day, and have not been im pressed with the results

Dr Modell Why is ammonium chloride included in the list?

Dr Travell In the occasional case, dramatic relief of pain is secured by the oral administration of ammonium chloride 0 5 to 1 Gm , 3 times a day The mechanism is unknown, but it might depend on the production of a diuresis and with drawal of fluid from the muscles

Dr Modell In acute coronary thrombosis, pain is some times unrelieved by morphine You mentioned that local block might be effective under these circumstances When should this form of treatment be applied?

Dr Travell We apply it whenever the agonizing pain of acute coronary thrombosis does not subside spontaneously If trigger areas can be found in the parasternal or precordial re gions, the injection of one or two of these tender points may terminate the pain at once so that no further analgesic medica tion is needed Just spraying the chest with ethyl chloride will sometimes accomplish the same result

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a patient I would spray the chest with ethyl chloride We have 3 cases in which the pain stopped at once and did not return

Dr Modell What part of the chest was sprayed?

Dr. Travell The front of the chest, especially the sternal and parasternal regions, and the precordium Special attention was paid to discrete localized areas of deep tenderness

SUMMARY

Dr. Gold The conference this afternoon dealt with one of the very common problems encountered in practically every branch of clinical medicine, namely, the painful spasm of skeletal muscles While painful spasm may occur in practically all muscles of the skeletal system, there are certain groups especially prone to become so involved, and these fall into certain fairly well-defined pain syndromes, known by a variety of names, such as lumbago, the frozen shoulder, and others Acute spasm in certain muscles, such as a sudden severe cramp in the calf which may awaken a patient out of a sound sleep, may cause pain directly over the area of the knotted muscle mass, but on the other hand many of the cases present more subtle problems, in that the pain is referred to an area distant from the site of the abnormal muscle In order to control these, it is imperative to locate the abnormal muscle giving rise to the referred pain, and in this connection it was pointed out that every muscle of the body has a specific pattern and area of reference which directs one to the muscle in spasm This muscle is identified by the fact that it possesses areas of deep tenderness, it shows a localized contraction when it is pressed, it causes pain when it is stretched The hypersensitive spots within these muscles, termed trigger areas, give rise to pain in the reference zones, when they are stimulated by pressure, cold, stretching, or needling

Four well defined technics were described for terminating painful spasm in skeletal muscles (1) the so-called local block methods, (2) stretching of muscles, with or without general

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Dr. Modell: Why is ammonium chloride included in the list?

Dr. Travell: In the occasional case, dramatic relief of pain is secured by the oral administration of ammonium chloride, 0.5 to 1 Gm., 3 times a day. The mechanism is unknown, but it might depend on the production of a diuresis and withdrawal of fluid from the muscles.

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Four well-defined technics were described for terminating painful spasm in skeletal muscles: (1) the so-called local block methods; (2) stretching of muscles, with or without general

anesthesia, (3) curarization, and (4) moist heat in the form of hot tubs It was pointed out that these are not mutually exclusive, and it was emphasized that additional measures are often imperative in order to secure the best immediate results as well as more lasting relief in problems of painful spasm In acute anterior poliomyelitis, the use of curare not only relieves the muscle pain but affords an opportunity for appropriate stretching of the affected muscles so as to prevent chronic shortening and deformities Some cases require salicylates and codeine as supplementary agents Attempts are made to reach such underlying causes as trauma, chilling of the body, chronic muscular strain resulting from hurry, repetitive movements, poor posture, and incorrect furniture design, impaired circulation as in anemia and intermittent claudication, low basal metabolic rate, tension and anxiety states which might yield to psychotherapy, chronic infection, and mechanical compression of nerve structures There seems to be some experience indicating that certain vitamins, such as ascorbic acid, nicotinic acid, and vitamin E, might have a place in these conditions, and intravenous procaine injections have been tried

While all of these systemic approaches and attempts at the control of underlying causes are of great importance, there remains the fact that in a large proportion of cases, underlying organic disease cannot be found, cannot be corrected, or does not exist, and the further fact that the most spectacular advance in the control of these painful and crippling skeletal muscle states has been made in the attempts at local relief of the spasm within the muscle itself The so-called local block technics received special attention, for these are accessible to the general practitioner for use in a wide variety of cases which he encounters in his office practice and in the hospital Their utility is based on the notion that in many of these painful spasms, a self sustaining cycle of spasm pain spasm, persisting long after the precipitating cause has vanished, may be

permanently abolished by interruption of a reflex mechanism Of the two technics, the successful infiltration of trigger areas in muscle requires considerable experience, it is not always easy to find the trigger areas The successful application of ethyl chloride spray would seem to require less skill, and may well lend itself to use by the intelligent patient himself Here then are simple forms of treatment from which a patient limping with a sprained ankle may walk off freely following a few sprayings with ethyl chloride, or a patient barely able to put on his coat because of an excruciatingly painful frozen shoulder may be able to swing his arm about freely following a few skillfully placed injections of procaine or a few sprayings with ethyl chloride, or a patient with acute coronary thrombosis and thoracic pain which does not yield well to morphine experiences prompt relief after a few applications of the ethyl chloride spray Clearly, not all cases respond, and in many the response is slow, incomplete, and only temporary, but there are those in whom these simple measures provide relief from pain and disability in a manner as dramatic as any experience one is likely to encounter in therapeutics

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Use of the New Antimicrobial Agents in Genitourinary Infections

Dr Walsh McDermott The treatment of infections of the genitourinary tract is the topic of the conference this afternoon The opening remarks will be made by Dr Victor Marshall

Dr Victor F Marshall The treatment of genitourinary infections has shown advances of unusual magnitude since the antimicrobial agents, such as the sulfa drugs, penicillin, and streptomycin, were put to work in this field Strange as it may seem, the very fact that these drugs are so potent as therapeutic agents has enhanced a source of danger which was of relatively little prominence in the days when no such effective remedies were available It is not a danger inherent in the toxicity of the agents That with the possible exception of streptomycin, is virtually negligible The real danger lies in an unfortunate state of mind resulting from the availability of highly potent antimicrobial drugs I refer to the dependence on the use of these agents alone as a means of bringing genitourinary infections under control The enthusiasm for these drugs is readily understandable since their effects are often dramatic and a source of intense satisfaction to both the physician and the patient, but it is the very fact of the striking results they produce, which brings into relief a fundamental error in the concept of therapy of genitourinary infections namely, the error that antimicrobial agents, if potent enough can solve the major problems relating to the cure of these

infections These drugs have modified therapeutic procedures and have made it possible to apply them more readily However, the basic principles have remained, and these cannot be successfully ignored One cannot emphasize too strongly that, while the new antimicrobial agents are very valuable as adjuncts in the therapy of genitourinary infections, accurate diagnosis and specific measures including surgery still continue as the mainstays of urologic practice

In this discussion I shall omit such items as the prophylactic use of these drugs after operation to prevent pneumonia I shall confine my remarks to those uses which relate to the genitourinary tract proper In this regard, 4 fairly distinct objectives may be discerned The first is the treatment of specific diseases such as gonorrhea Since this represents a special problem which should serve as the topic of a separate conference, I shall omit it from the present discussion The second is to reduce the acute quality of some infections The third is to reduce the activity of many subacute and chronic infections The reduction of the activity of acute, subacute, and chronic infections is especially applicable to the preoperative preparation of many urologic patients The fourth is to aid in clearing infection after the underlying pathologic lesion has been corrected by specific measures, or by nature It is well to bear in mind that some patients recover without any therapy

In regard to the matter of complete urologic investigation, there is the question whether all patients with urinary infection should be subjected to it There is also the question as to the particular time a detailed urologic study is best undertaken While most of you can recall cases of simple infections which were managed successfully with simple therapy, the urologist can cite many instances of that kind which proved deceptive and concealed a serious disease, even cases in which simple therapy seemed to be entirely successful, but only temporarily so Such experiences give indication of the danger,

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the investigation may also prove essentially negative and present no suggestion of stone, tuberculosis, or tumor. Under these conditions one is apt to conclude that there is no obstruction, but I believe there is obstruction in most of such cases, at least in the sense of impaired drainage of the urethral glands.

It is well known that in order to ascertain the value of a drug, it is necessary to compare the course of patients receiving the particular agent with the course of a group which serve as controls. Such studies of antimicrobial agents in urologic infections present unusual difficulties. These difficulties are reflected by the large number of faulty reports in the literature. I might mention a few of the common defects. Controls are either absent or their numbers too small, the total number of cases may be too few, the extent and duration of the follow up may be inadequate or too brief and fail to reveal the true course of response, whether temporary or permanent. In judging the utility of an antimicrobial agent in urinary infection, the fact that an appreciable number of cases undergo spontaneous recovery is a common source of error. The variables in the treatment of urologic infections are so numerous that it is quite impossible to secure satisfactory data from reasonably comparable groups without intensive selection and large numbers of cases. A small series of urologic patients usually fails to provide enough material for a control group and a treated group that are sufficiently alike to supply data for valid conclusions. Variations are extremely wide in the kind and degree of underlying pathology which plays a most important part in determining the response to the antimicrobial agent. There is also the fact that during the use of the antimicrobial agents, the patients included in study groups are often receiving simultaneous treatment for the underlying lesions, thus adding further elements of uncertainty in the evaluation of the particular drug.

I may now say a few words about the various antimicrobial

the hazard of the false sense of security provided by highly effectual antimicrobial drugs in infections of the genitourinary tract

An adequate history and careful examination may yield specific clues, such as a large mass in one flank, gross hematuria, or the like, which would indicate the need for an elaborate urologic investigation But even when such clues are not obtained, I would suggest that any urinary infection which does not respond promptly, completely, and permanently to simple therapy should be investigated further These points may be used as a practical means for drawing the line which divides urologic patients into 2 classes those that are to receive relatively simple treatment without detailed urologic investigation, and those in whom an elaborate urologic study is imperative In the therapeutic test, 'promptly means within a week, "completely" means the absence of residual symptoms and signs with a clear urine on microscopic examination, and 'permanently" means the absence of a tendency to recurrence

Among the factors in the urinary tract which lead to infection that is not promptly completely, and permanently eradicated by simple therapy, four are most common obstructions, foreign bodies including calculi, neoplasms, and tuberculosis It is these that one should search for whenever an infection shows inadequate response There are a few factors which are relatively rare, namely, specific diseases like syphilis and blastomycosis, and radiation injury Conditions which interfere with the complete success of simple therapy are sometimes obscure An example is the case of the female who presents urgency and frequency with inadequate response to simple therapy In such a case, the urine is often found to be clear, cultures of the urine may be substantially negative, only slight trigonitis or granular appearance of the mucosa may be revealed by cystoscopy, instruments pass freely, the patient passes urine freely, and may present no residue The remainder of

serious I do not recall a case in which it failed to subside promptly after the medication was interrupted

A word about the sulfa drugs They clear about 90 per cent of uncomplicated bacilluria They attack a wide range of organisms They are effective whether the urine is acid or alkaline They are somewhat more effective when the urine is alkaline and, unlike mandelic acid, they are of some use in infection with the B proteus which splits urea and causes highly alkaline urine It is a noteworthy fact that they often seem beneficial in urinary tract infection with organisms known to be not especially susceptible to these drugs Also, the effective dose in urinary tract infection is often smaller than would be expected in the case of a similar infection outside the urinary tract That the drug is not only in the tissues but in the urine which washes the internal surface of the urinary tract, has been offered as an explanation, but it may not be so simple as that

The action of penicillin seems to be quite specific for organisms in the urinary tract Those that are not susceptible to penicillin are not affected in the urinary tract either However, it is necessary to remember that in the urinary tract infections are not infrequently mixed, and that the mixed infection is not always recognized as such There is also the fact that organisms which grow best in the patient are not necessarily the ones which grow best in the laboratory with the particular method used Accordingly, a trial of penicillin in obstinate cases is occasionally worthwhile, even though the infection seems to be due to a type of organism not generally considered susceptible If by this method, one of the members of a mixed infection, which may have escaped detection is reduced or eradicated, it may help the patient overcome the remaining infection

Streptomycin is a potent weapon against Gram negative bacilli which are very common in the urinary tract However, there are 2 factors which limit its application One is the

drugs which are administered in association with measures for establishing the diagnosis and for the management of the underlying causes responsible for the infection The number of antimicrobial drugs is very large, but only a few of them are sufficiently important to merit consideration

Methenamine, better known under the trade name of Uro tropin, is one of the older urinary antiseptics It can be taken over periods of several weeks Perhaps its greatest usefulness at present is in the tapering off of antiseptic therapy during the periods when final healing is proceeding after major infectious activity has been eradicated or nearly so Its action depends on the liberation of formaldehyde It is effective only in an acid urine Its antiseptic action is not very potent, but also not specific, and it may be used against a very wide variety of organisms

Mandelic acid is a valuable urinary antiseptic There has been a tendency to displace it with some of the newer anti biotic agents, but there are conditions in which it has not been possible by means of other antibiotic drugs to produce equally satisfactory results It is most effective against organ isms of the colon group Highly acid urine is unfavorable to the growth of bacteria Mandelic acid is excreted in the urine and produces its antiseptic action, at least in part, as the re sult of urinary acidification The discovery that betahydroxy butyric acid was the bactericidal agent in the urine during the use of the ketogenic diet led to the investigation of other hydroxy acids and to the discovery of mandelic acid as a po- tent urinary antiseptic about 15 years ago When mandelic acid fails to produce the expected results, it may be due to the fact that the pH of the urine is not below 5 5 and the concen tration of the drug is not above 0 5 per cent Mandelic acid produces a few minor toxic effects The doses of 10 to 12 Gm daily which are necessary may cause gastrointestinal upsets Renal irritation is one of the common toxic effects It is de- tected by red blood cells and albumin in the urine It is rarely

serious I do not recall a case in which it failed to subside promptly after the medication was interrupted

A word about the sulfa drugs They clear about 90 per cent of uncomplicated bacillurias They attack a wide range of organisms They are effective whether the urine is acid or alkaline They are somewhat more effective when the urine is alkaline and, unlike mandelic acid, they are of some use in infection with the B proteus which splits urea and causes highly alkaline urine It is a noteworthy fact that they often seem beneficial in urinary tract infection with organisms known to be not especially susceptible to these drugs Also, the effective dose in urinary tract infection is often smaller than would be expected in the case of a similar infection outside the urinary tract That the drug is not only in the tissues, but in the urine which washes the internal surface of the urinary tract, has been offered as an explanation, but it may not be so simple as that

The action of penicillin seems to be quite specific for organisms in the urinary tract Those that are not susceptible to penicillin are not affected in the urinary tract either However, it is necessary to remember that in the urinary tract infections are not infrequently mixed, and that the mixed infection is not always recognized as such There is also the fact that organisms which grow best in the patient are not necessarily the ones which grow best in the laboratory with the particular method used Accordingly, a trial of penicillin in obstinate cases is occasionally worthwhile even though the infection seems to be due to a type of organism not generally considered susceptible If, by this method one of the members of a mixed infection, which may have escaped detection, is reduced or eradicated, it may help the patient overcome the remaining infection

Streptomycin is a potent weapon against Gram negative bacilli which are very common in the urinary tract However, there are 2 factors which limit its application One is the

occasional but severe toxic effects The other is the marked tendency for the development of streptomycin resistance It is our present practice in urology to reserve streptomycin as an ace in the hole for use after the other tricks have been played

Before I go further, and some may wonder about this, I might mention that there is still some use for the arsenicals in urology, not only against spirochetal infections, but against certain other stubborn infections, particularly those due to staphylococci The value of the arsenicals is not firmly established, but once in a while they seem to produce strikingly favorable results

The value of renal and vesical lavage in urinary infections is not likely to go unchallenged It is often stated that urologists are forever washing bladders and kidneys, and putting in various colored solutions in the belief that they are producing cures It is pointed out that the organisms are in the tissues where the antiseptic solution cannot reach them unless the solution destroys the tissues This, of course, is true, but it does not reveal the whole picture The lavage washes out foreign material, such as pus, bits of urinary sediment, and calcified and phosphatic debris Drainage from the surface is thus improved, and drainage is of the greatest value in the treatment of infections Organisms grow in the urine as well as in the tissues This is especially true if there is residual urine The residual urine is warm, as in an incubator Since it is never completely drained out, it provides especially favorable conditions for the continued growth of the organisms in the urine as well as in the patient's tissues Instillation adds a bacteriostatic quality to the residual urine, even if it is only temporary Also, the instrumentation which is necessary for renal pelvic lavage, and more particularly for bladder lavage, may in itself temporarily improve drainage

Dr McDermott I find myself in essential accord with Dr Marshall's remarks on the subject of the antimicrobial ther-

apy of urinary tract infections. I have one minor point of dissent, Dr. Marshall. I believe that the use of the arsphenamines is purely a matter of adherence to a tradition. With everything else I most heartily agree.

It cannot be too strongly emphasized that in antimicrobial therapy, whenever the anatomic situation is such that healing is impossible, the administration of a drug accomplishes no more than temporary inhibition of the infection. Even if sterilization results, when the anatomic condition is one that favors infection, infection will inevitably recur. I wonder whether Dr. Marshall would agree with me on the point that the mere presence of infection in the urinary tract signifies at least a temporary morphologic defect in the tract. An infection established there then perpetuates the abnormality.

Dr. Marshall's reference to the difficulty of evaluating the various forms of antimicrobial therapy in genitourinary infections is a particularly important matter. One simply does not encounter comparable cases in sufficient numbers to enable one to secure the most satisfactory kind of data for this purpose.

I would like also to refer to the problem of the concentrations of a drug in the urine. To be sure, infections are in the tissues, so that theoretically at least, high concentrations of the drug in the urine would serve no useful purpose, and the significant matter would be the concentration in the extracellular fluid, as reflected by that in the blood. In his study of streptomycin, however, Dr. Finland showed quite convincingly that, when the urine is alkaline, streptomycin-resistant variants do not emerge to anything like the same degree as when the urine is maintained acid. That observation indicates a peculiar relation between urinary infection and the composition of the urine. It might be that, as Dr. Marshall pointed out, infections can be propagated by the bacteria in the urine. They might multiply in the urine and invade the tissues from there. I think we may have to give more critical

thought to the prevailing belief that what is in the urine is of no consequence

May we now have some questions from the audience?

Dr Harry Gold I might ask Dr Marshall what he would suggest as the first drug a general practitioner should prescribe for a patient in his office who has had urinary symptoms with infection for several days Let us assume that the doctor has examined the urine and has found clumps of pus cells, but that the remainder of the examination provides him with no additional information, and, further, that he is not in a position at the moment to start a more intensive exploration of the genitourinary tract Which of the drugs he mentioned would most likely prove successful?

Dr Marshall I am glad you emphasized the diagnostic aspects There are a lot of little things that anyone can do without special equipment A two glass or three glass test supplies some indication of the site of the infection As you know, the first glass represents the bladder urine plus the urethral washings The second glass represents the bladder urine minus the urethral washings The third glass represents the bladder urine plus what can be squeezed out of the prostate A stained smear can be made in the office, and this will show something about the type of infection

To come back to your specific question, we usually give a sulfa drug and most often sulfadiazine This drug is not very expensive All the patient has to do is to swallow a few tablets We usually start with what is considered a small dose, 0 5 Gm four times a day, because it keeps low the incidence of complications If the patient fails to show some response in a day or two, it is an indication that further diagnostic tests are required

Dr McDermott What would you think about the use of streptomycin in such a situation?

Dr Marshall I am against that for several reasons In many cases, streptomycin will suppress the urinary tract infection,

and the patient will seem to have recovered Even though the doctor knows better and is not lulled into a false sense of security the patient may misinterpret the results and fail to return for the various diagnostic tests Another objection is the fact that some of these patients may need streptomycin later, and when they need it most, they may fail to respond be cause the first course made their organism resistant to the drug We have had this matter brought forcefully to our at tention in 2 cases of uretero intestinal transplantation Re ports in the literature indicate that the bowels can be cleaned up with sulfasuccinidine and sulfathalidine, together with a little streptomycin and thus reduce the number of bacterial organisms We tried it in these 2 patients When we dis continued the streptomycin about 2 days after the opera tion both of them developed a fulminating and fatal pyelone phritis The degree of obstruction to the kidneys was not very great Two cases do not prove very much but our experience in these was enough to make us cautious And so we do not use streptomycin as a routine measure We generally give sulfadiazine, penicillin mandelic acid or other agents first, even if the infection is a Gram negative bacillus When we have decided that the time has come to hit the infection with all we have we then turn to streptomycin

Dr McDermott Would you say it is not proper to give streptomycin for urinary tract infections until a complete and exhaustive work up has been made and a decision has been reached concerning surgical measures?

Dr Marshall That is correct It is well to know what the whole problem is before using streptomycin I think the ad ministration of streptomycin just because the patient has a few symptoms or some pus cells is a very dangerous business

Dr Walter Modell I think it is quite generally stated that penicillin is not especially useful in infections of the urinary tract This is not the first time I have heard Dr Marshall say that penicillin is useful I wonder if he would amplify that

the urethra These are localized and are not especially important

Dr McDermott Let us assume, in this hypothetic case, it could be proved that the infection is higher up This might be established by comparing catheterized and noncatheterized specimens Do you think that such an infection, somewhere high in the urinary tract, might subsequently lead to hypertension? Would detailed investigation be justified on this basis? What would you think about that, Dr Humphreys?

Dr Gustavus A Humphreys I have no convictions one way or the other on that subject

Dr McDermott I am concerned about hypertension associated with renal infection What I am trying to get at is this Can there be urinary tract infection so indolent and so asymptomatic that a considerable amount of renal function might be lost over a period of several years? Or is such infection always fairly obvious?

Dr Marshall It is not always obvious, but in chronic pyelonephritis there is usually an increased number of pus cells in the urine, or the history is one of recurring clinical episodes The condition may not be evident at one visit, and the urine may even be crystal clear when it is held up to the window

Dr Modell Does Dr Marshall use the mixture of three sulfonamides?

Dr Marshall I know it is a popular mixture but I have not used it It is supposed to prevent crystalluria We have had very few cases of this since, from the early days of the use of the sulfa drugs, we have given large doses of sodium bicarbonate simultaneously That effectively prevents precipitation Furthermore, as I mentioned before, we are inclined to use very small doses of the sulfonamides 0 5 Gm 4 times a day

Dr Gold I wonder whether Dr Marshall has had any experiences in which urinary infections failed to respond to

treatment with sulfonamides given for a week or two but then cleared up on treatment with Urotropin or mandelic acid?

Dr Marshall Yes We have seen quite a number of those

Dr Laurence B Hobson What has been the experience with avoiding the production of resistant organisms by using streptomycin simultaneously with other therapy, say a sulfa drug?

Dr Marshall I think Dr Tompsett can tell you more about that As I have said, we use streptomycin only occasionally, and then as a final measure

Dr Tompsett I think everyone wants to know the answer to that question We do not have it

Dr McDermott However, Dr Tompsett do you think it makes sense on the basis of our present knowledge to use sulfadiazine with streptomycin? Is there any theoretic basis for combining the two drugs?

Dr Tompsett In theory any organism in the urinary tract or elsewhere has a certain incidence of mutants resistant to streptomycin which may develop during the process of mul tiplication similarly, in the case of the sulfonamides In theory, the incidence of organisms which would be resistant to both would equal that of the first multiplied by that of the second For example if the incidence of streptomycin resistant mutants was one in a billion and of sulfonamide resistant mu tants was also one in a billion one would expect the incidence of organisms resistant to both would be the product of the two in other words one billion times one billion On the basis of this theory if an organism were sensitive to both sulfadiazine and streptomycin attacking it with both drugs simultaneously should markedly lower the chances of developing a resistant strain The trouble is that we are not certain whether it really works that way

Dr Modell What dose of Urotropin do you give? What is the routine?

uncomplicated It represents simply a good inoculation Such infections occur in the best of hospitals where any considerable number of cystoscopies are performed An important point in this connection is the fact that the organisms implanted are more regularly the aerobacter, proteus, and pyocyaneus groups than was the case 10 years ago These are resistant to practically everything we have

Dr McDermott That is an extremely significant point I am very much interested in what you have said about the change in prevalence, for it has an important bearing on the use of antimicrobial agents Aureomycin is a potent agent against the Gram negative bacilli In many who have been treated with aureomycin, the infection becomes predominantly proteus which, as Dr Humphreys pointed out, is one about which little can be done There may be such a balance of organisms in the genitourinary tract that, with a particular anatomic situation and infection, upsetting one may actually promote development of the other Pyocyaneus and proteus may well become a serious problem

Dr Marshall That is a real difficulty Even when the urologist eliminates the stones and obstructions a well established proteus infection within the kidneys leaves us with a problem for which there is no very effective therapy

Dr McDermott Streptomycin is effective in aerobacter infections provided it has not been previously misused I think we are in complete agreement that this short time, potent, antimicrobial agent should be reserved until everything has been cleaned up, and put to use when future infection is no longer inevitable

I would now like to say a word or two about Dr Gold s question

Dr Gold Might I repair the question a bit?

Dr McDermott I like it the way it is if you have no objection I would treat this infection with the most potent agent, and that is streptomycin, if the infection seemed a seri

ous threat to the chance of recovery from the heart attack On the other hand, if the infection did not introduce a danger of this kind, I might be inclined to let it go without special treatment in the hope that it would take care of itself Would you agree with that?

Dr Marshall I believe that even in a condition of that kind I would withhold streptomycin unless the situation were critical I would probably prescribe penicillin and sulfa drugs, and then taper off the treatment with mandelic acid I would simply attempt to hold the infection in check

Dr McDermott I presume that, in withholding streptomycin, it is your thought to proceed in a conservative manner, since the obstruction present in these cases may clear up in a few days Is that it?

Dr. Marshall Yes

Dr Gold Dr Marshall's suggestion of tapering off the treatment with mandelic acid leaves me wondering why one would wish to diminish the infection gradually, which is the notion conveyed by the term taper off' I can see the wisdom of using all three drugs, and also the reason for not using them simultaneously, the sulfa drugs being most effective in an alkaline medium while mandelic acid is most effective in an acid medium If that were not the case, it would seem to me proper to use both of them at the same time I can see no advantage in damaging the bacterial population slowly and gradually over wrecking it as completely and rapidly as possible, assuming the absence of a special source of danger in the rapid destruction

I think I should proceed with my original purpose of repairing my question I had suggested that the urinary infection which develops after catheterization in an individual with urinary retention following the use of morphine is a simple infection without obstruction, and I asked how that is best treated There seems to be agreement on the point that these cases are not simple and do have obstruction And

uncomplicated It represents simply a good inoculation Such infections occur in the best of hospitals where any considerable number of cystoscopies are performed An important point in this connection is the fact that the organisms implanted are more regularly the aerobacter, proteus, and pyocyaneus groups than was the case 10 years ago These are resistant to practically everything we have

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of the major organism responsible for the infection Streptomycin is an important weapon against Gram negative bacteria, but there are important limitations to its use Because of the occasional toxic actions and the ready development of streptomycin resistant organisms, it was strongly recommended that this drug be reserved for use until obstruction or other anatomic defects are eliminated, and future infection is no longer inevitable

A number of problems in the management of genitourinary infections were raised in discussion These included the possible role of high drug concentration in the urine in contact with infected tissue, the possible value of arsenicals against staphylococcus infection, the question of the timing of antibiotic therapy in relation to the correction of anatomic abnormality and the extent to which the condition should first be investigated, the use of sulfonamide mixtures, the possibility of reducing the incidence of streptomycin resistance by the simultaneous use of sulfa drugs, and the question of increased sensitivity of the aged to the toxic actions of streptomycin Evidence bearing on these problems was cited but in most cases the available information was not adequate for a final answer

Management of the Menopause

Dr Ralph W Gause The subject for today is the treatment of the menopause But before introducing the speaker, I should like to express a personal opinion which I hold with firm conviction I strongly believe that the menopause should be treated by the doctor who knows the patient best not necessarily by one who knows the disease best The patient s emotional state and personal problems are more important than medicines And they are much harder to manage than the purely medicinal problems The doctor who knows the patient well and who has inspired the patient with confidence in him is the one to treat her menopause Beyond that, it is a matter of indifference whether he is a general practitioner or surgeon or anyone else A woman s reaction to the menopause is variable and individual Therapy must be varied and individualized to the same extent

And now, Dr Shorr

Dr Ephraim Shorr It seems that about every four years I am asked to talk about the menopause When the topic was suggested for this conference, I reviewed an article of mine published in 1940 and I compared the text with our knowledge of the subject as it stands at the present time I was chagrined to discover how little I had learned in that period I therefore thought that if I were to start with that paper and indicate the changes which have resulted from the enlarged experience, I could at least make a progress report on the subject

What is the menopause? It appears to be the consequence

cancer, suggested that there was no appreciable danger in the use of the small amounts of estrogen which might be necessary to relieve the symptoms of the menopause in a patient with cancer. We are seeing an interesting shift in the views on the relationship of exogenous estrogens to neocarcinogenesis. Perhaps I should elaborate on this point because there is so much fear of the hazard of inducing cancer by the estrogens. Hartman and others, at Yale, administered massive doses of estrogens to monkeys for a number of years. Some received as much as 1,000,000 rat units a year. There was not a single instance of carcinomatous change in any organ. The close relationship of the monkey to man makes these experiments particularly valid in evaluating the dangers of estrogens in humans. However, there is one observation which leaves this problem still undecided, namely, the evidence which suggests that, while the administration of estrogens is not likely to produce cancer in humans, these compounds may prove harmful in women in whom a carcinoma of the breast has already developed.

While we are on this subject, I might mention the need for bearing in mind the matter of pelvic malignancy which arises coincidentally with the menopause. I should stress the desirability of making thorough pelvic examinations before one starts estrogen therapy in the menopause, and for repeating the examination periodically during the course of the treatment. The reason is that menstrual irregularities may be attributed to the menopause when the real cause is cancer.

Bleeding is one of the problems of estrogen therapy in the menopause. It occurs most often after the drug is discontinued following a period of treatment. It can be minimized or prevented by the appropriate plan of therapy which takes into account the length of time the estrogen is given and the size of the dose. The duration of treatment should be inversely proportional to the dose. Thus, if a patient receives full biologic replacement dos[illegible], be continu[illegible]

a period of three or four weeks A rest period then follows, and when the drug is resumed, smaller doses may be given, and these may be continued for a longer period before another rest period The intermittent plan of therapy is the most favorable one for reducing or preventing withdrawal bleeding The rest periods permit gradual involution of the endometrium They also have the advantage of allowing periodic evaluation of the spontaneous adjustments the patient is making to the menopause

We are in agreement with the view expressed by Dr Gause to the effect that emotional and psychologic factors play a major part in the reaction of women to the menopause Maladjustments before the menopause have a tendency to increase difficulties during the menopause We have been impressed by the high frequency of the menopausal syndrome in patients with unfavorable emotional adjustments combined with unpleasant personal situations, and we have been equally impressed with the frequency of complete relief of symptoms when personal stresses and maladjustments are corrected The return of menopausal symptoms two or three years after an apparent adjustment has been made can often be assigned directly to exciting factors in the patient s life situations

Dr Gause Thank you, Dr Shorr

From my experience as a gynecologist, I am in complete accord with Dr Shorr s view that there is little danger of estrogens promoting the development of cancer

Perhaps we should have a few words on the psychiatric aspects of the menopause Dr Ripley, would you say something about that?

Dr Herbert S Ripley Many women look upon the menopause as a period when their sexual life is on its way to the end, or as a period of transition to the status of 'old women' In many, the realization that the changes associated with aging are taking place is the cause of psychologic trauma Inability

Dr Thomas We give them orally or parenterally Preparations are available for both routes We employ materials that have been standardized in terms of rat units The standardization is carried out by both the oral and parenteral routes The doses expressed in rat units refer to the oral or the parenteral method of standardization, depending upon the route which is being used in the treatment of the particular patient As I have stated, an attempt is made to use enough of the drug to establish full estrus, and it may take 6 weeks of treatment to reach that point We determine the degree of symptomatic relief at this dosage level We then reduce the dosage in steps each new level being maintained for a period of 3 weeks In that way, we establish the minimal dosage required to maintain the maximal relief

Dr Gause What do you mean by the "three week periods ?

Dr Thomas The patient is maintained with a reduced dosage for 2 weeks, followed by 1 week of rest The dose is then again reduced, continued for 2 weeks, and again followed by 1 week of rest This system of reduction of the dosage is continued until the desired level is reached.

Dr Gause Thank you, Dr Thomas

Are there any questions for Dr Shorr?

Dr Gold I should like to ask a question pertaining to the selection of preparations The estrogen materials produce several effects—changes in the smear, changes in the subjective symptoms, and so on One patient may, for example, suffer with severe headaches, and another with severe flushes and sweats Does the pattern or the spectrum of the action of different estrogenic materials differ? Is there any basis for the selection of estrogens in relation to these or any other manifestations of the menopause? Are some of the actions better developed in the molecular structure of one estrogen, and other actions better developed in the structure of another estrogen? In relation to the adrenal cortical hormones, it is well known that some exert a dominant action on sugar

metabolism, while others exert a greater action on the electrolytes Is there anything analogous to that in the case of the estrogens?

Dr Shorr That is a very important point, Dr Gold Obviously, the best preparation would be one which could provide symptomatic relief without any biologic estrogenic effects, that is endometrial proliferation, bleeding etc Reports have appeared from time to time suggesting that such a dissociation has been achieved in the case of a particular product However, the fairly extensive experience which we have had in the use of the estrogens has convinced us that potency with respect to symptomatic relief runs parallel with potency as revealed by the vaginal smear We have studied ten or twelve different preparations in considerable detail, and the results leave us with little doubt that no one of the preparations possesses superiority in respect to the relief of symptoms over any other, which is not associated with parallel superiority in biologic potency We believe that the choice of an estrogenic hormone in therapy should be made on the basis of cost freedom from unpleasant side effects or toxic effects, and ease of administration Generally speaking a natural estrogen, the cost of which is sufficiently low to enable the patient to use the oral route, would be the preparation of choice The oral route is convenient, and when the daily requirement is taken in 2 doses, one in the morning and one in the evening the efficiency of the dosage is increased The reason why this is not usually done is the fact that estrogens are less effective after oral administration and to employ this route larger doses are required Some natural estrogens are too costly to permit this

Dr Gold Do you think all the natural estrogens are superior to the synthetic ones?

Dr Shorr The advantage lies in the fact that the synthetic products are more active with respect to undesirable side effects, and that some patients who require large doses can tolerate only the natural estrogens

principle employed, wherever possible, in U S Pharmacopeial bio assays We therefore no longer say that the potency of a given compound is so many milligrams per kilogram of animal, but that the potency of the compound in question is equal to, or 50 per cent of, or 75 per cent of, the potency of a standard material with which the unknown is compared Not all materials can be assayed in accordance with this principle, because a standard is not available for the comparison in the case of all materials But where there is a standard, no doubt remains that the most reliable information about the potency of an unknown is obtainable when the unknown is compared with the standard That is why I questioned your dependence on a 'rat unit' as an expression of the potency of an estrogen in the place of a U S P Unit or an International Unit

There can be no doubt of the soundness of the point made by Dr Cattell, namely, that drugs should be prescribed in terms of weight or volume rather than in terms of biologic units wherever possible However, there is considerable evidence favoring the validity of the position taken by Dr Shorr to the effect that the correlation between biologic activity and weight of material in the case of the estrogenic compounds is not sufficient to use these materials in terms of their weight There is fairly strong indication that, for example, 1 mg of each of two estrogens, which may produce equal effects by parenteral administration in the mouse or the rat, may produce effects which differ widely in their intensity when the two are compared by oral administration in humans This may result from differences in the extent of their absorption and speed of elimination in the different species

Dr Gause Dr Shorr, you stated that you prefer the oral route, but do not some patients require parenteral administration in order to obtain symptomatic relief?

Dr Shorr I see no reason why the oral route cannot meet all the requirements

Dr. Gause: It is my experience, however, that some patients fail to obtain the same degree of symptomatic relief with the oral doses that they do with parenteral treatment.

Dr. Shorr: This observation of yours may be explained by the psychologic factors which are introduced by an injection of a drug. These are important features, especially in those patients whose menopausal symptoms may be chiefly of psychic origin rather than the result of estrogen deficiency. Such patients may obtain relief from the injection of anything.

Dr. Janet Travell: Is there any oral preparation that you particularly prefer?

Dr. Shorr: We commonly use Premarin which is chiefly estrone sulfate, although not completely pure. This is a natural hormone. It is not excessively costly, 7 to 10 cents for a tablet of 1.25 mg., equivalent to 800 rat units.

Dr. Nathaniel T. Kwit: When you use estrogens parenterally, what is the interval between injections?

Dr. Shorr: It varies a great deal. The more frequent the injection, the smaller is the dose required for a particular effect. The injection of 10,000 rat units once every 10 days is a much less efficient way of using the drug than 500 rat units twice a day.

Dr. Gold: I assume that the reason for the low economy of the very large dose at one time is due to the losses by excretion of a large share of the material before there has been an opportunity for it to exert its action.

Dr. Shorr: That is correct. When an excessive amount is given at *one time, most of it is ineffectual, being inactivated* chiefly in the liver. Estradiol, for example, is converted into estradiol glycuronidate, which has only 1/600 of the estrogenic activity of the original compound.

Visitor: Dr. Ripley mentioned the increase in sexual tension which may occur in estrogen therapy. Is not libido generally increased in the menopause?

Dr. Ripley: Occasionally it is, but most commonly sexual-

also knows how great this difference is We must not confuse this problem with the problem of bio assay and differences in potency of preparations

Dr Travell Estrogens, then, present the same problems as preparations of liver There are the units for oral administration and the units for injection The dose may, for example be 10 units in either case, but the oral and injectable units are not the same, an oral unit containing much more of the potent material than the parenteral unit

Dr Shorr That is correct

Dr Gold That method of dealing with liver preparations is justifiable because both the oral and the injectable materials are impure and are not available in forms suitable for expression in terms of milligrams The case with the pure estrogens, however, is different, for they are available in the form of a pure crystal, and that makes it possible to express whatever amount is given by whatever route it is given in terms of milligrams

Dr Alexander R Stevens, Jr What proportion of patients who respond well to Premarin would show equally satisfactory response to stilbestrol?

Dr Shorr I do not have that information I might cite the observation which we made some years ago in a study of stilbestrol in a group of patients in which some required small and others large doses We found that among those requiring the large doses between 25 and 40 per cent developed toxic symptoms Whether stilbestrol can be substituted for the natural hormone depends on the dose which the patient needs for satisfactory therapeutic results Among patients whose dosage requirement is small, it is probable that the incidence of satisfactory results will be as high with synthetic as with natural estrogens

Dr Walter Modell What is the dose of stilbestrol in terms of biologic units?

Dr Shorr The estrus unit of stilbestrol is 1 5 to 3 mg I

should say that 1 mg of stilbestrol given by mouth would be approximately equivalent to the effect of 1,200 rat units

Visitor What dangers are there in the use of the estrogens?

Dr Shorr The occurrence of permanent injury is not well established and is on the whole, negligible There are effects from overdosage, often unpleasant, such as disagreeable tenderness of the breasts, excessive endometrial hyperplasia, and bleeding

Dr Cattell Is it possible to prolong menopause by continuous therapy over long periods?

Dr Shorr I don t think we can view it that way if what we are doing is to relieve the patient s symptoms If the woman is enabled to cope with her anxieties and unpleasant life situations more effectively, the therapy should serve to shorten her period of disability

Dr Cattell But do the physiologic adjustments of the menopause continue on during the therapy?

Dr Shorr I believe that treatment allows them to go on In the intermittent form of therapy which was mentioned earlier, there is indication during the rest periods that adjustments are being made

Dr Gold I have never heard of any systematic studies to compare the duration of the period of menopause in the treated and untreated patient It might be difficult to determine with precision the beginnings and endings However, Dr Cattell s question strikes me as a rather significant one When the patient enters on the course of the menopause, mechanisms for bringing about adjustments are probably set in operation, and without proof to the contrary, it would seem to me possible that the evolution of the whole process might be delayed by factors which control some of the disturbances and thereby reduce the stimulus to spontaneous adjustments For example, patients with anxiety states are often relieved by change to a less challenging environment, but, while the patient enjoys considerable relief, there is indi

the impression that little has been learned of treatment of the menopause in the past 10 years From this one is not to infer a want of highly effective methods of treatment The greatest problem in this field is the failure to utilize all the available means of treatment In particular, insufficient attention is paid to the psychiatric phases of the menopause and to the need for individualizing the therapy to meet the special needs of particular patients Hormones of high potency are avail able, both synthetic and natural estrogens and androgens We believe that the drug of choice is a natural estrogen by oral administration In the vaginal smear, we have an excellent guide for the control of dosage The hormones exert a specific effect, and there is little danger in their liberal use The risk of producing cancer seems to be without foundation

Dr Gause I am sorry that we are unable to take on any more questions because our time has run out.

SUMMARY

Dr Harry Gold · Considerable ground was covered this afternoon in the conference on the treatment of the meno pause. The discussion involved both theoretic and practical issues and threw light on a large number of problems Who is best equipped to treat the menopause, the relation between the symptoms of the menopause and the disturbance in hor mones, the use of estrogens and androgens, and combinations of the two, estrogen therapy and cancer, the vaginal smear, the psychiatric disturbances of the menopause, the choice of preparations of estrogens, dosage, and route of administra tion, natural versus synthetic estrogens, regimen for treat ment, sources of confusion in the bio assay of estrogens, and the question whether estrogen therapy prolongs the meno-pause.

The essential hormonal changes involve a urinary increase in gonadotrophic hormone of the pituitary and a marked re duction in circulating estrogen The estrogen deficiency is

the factor which appears to be related to the menopausal symptoms. The significance of the psychologic aspects of the menopausal syndrome was stressed, from the standpoint of their role in the severity of the symptoms and the response to treatment. The patient's emotional and personal needs are considered more crucial than her medicinal needs. Nevertheless, substantial improvement may be anticipated from the appropriate use of the estrogens. Attention was called to the utility of these drugs in some cases of involutional depression related to the menopause, and signs to differentiate these from cases not likely to respond were pointed out. The natural estrogens were preferred on the basis of the fact that, where large doses are necessary, they are less apt to produce disagreeable side effects than synthetic stilbestrol. It was pointed out that smaller doses at more frequent intervals are more effective than massive doses at very long intervals. The oral route was preferred, and the belief was expressed that the alleged superiority of the parenteral route is due to the psychologic effect of an injection. The vaginal smear was described as an extremely valuable guide to estrogen therapy. A plan of intermittent treatment was outlined which ensures that the full benefit of the drug is obtained. In this regimen the estrogen is administered until full replacement is observed in the smear, and then the dose is reduced by steps in the endeavor to establish the smallest dose which maintains the optimum state of improvement in menopausal symptoms. There appears to be no significant danger of cancer in the use of the estrogens for the treatment of the menopause. Attention was called to the need for pelvic examinations to ensure that bleeding due to cancer unrelated to the treatment may not be mistaken for an effect of the estrogen.

to the hospital for treatment and remain there until they are pronounced cured by the medical staff After arrival at the hospital these patients are all treated alike from the medical standpoint However, some differences in the custodial regulations arise because of differences in their legal status

On arrival the patient is taken to the admission room for the first physical examination, which is brief but careful After it has been determined that the patient has brought in no contraband, he is examined for gross physical defects cardiac pulmonary, or nervous disorders, and contagious diseases Particular attention is also paid to evidence of active physical dependence on the drug This is not a simple procedure There is no way of proving that a patient is dependent on morphine except by watching for withdrawal signs which appear in such patients when morphine is withheld These appear within 30 hours or less from the time of the last dose If for some reason, medical, legal, or other, one wishes to demonstrate that a patient is physically addicted to opiates, he must be studied in a controlled environment under constant observation for 1 or 2 days Only if the characteristic withdrawal signs appear can one state that the patient is physically dependent on the drug We do not usually have to subject the patient to this procedure at the time of his arrival, but we do try to observe other, though less conclusive, signs of active addiction

Of these, constriction of the pupils is probably the most significant This may be present if the patient has had morphine recently—that is within several hours before admission to the institution There may also be some degree of stupor or other evidence of the narcotic effects of the drug We also look for fresh needle marks These may be the result of subcutaneous injection, in which case they usually appear on the lateral aspects of the arm or thigh, or of intravenous injection, in which case pigmented scars may be seen in the antecubital fossae or elsewhere A brief history is taken with particular reference to addiction, namely, the time of onset of addiction,

not continued over 5 days We are always careful to watch for symptoms of toxicity due to bromides An important adjunct to the treatment, which is not concerned so much with the physical dependence symptoms but with the general behavior and condition of the patients, is vitamin therapy These patients are frequently undernourished or at least suffer from malnutrition in the sense that their diet has been poor in vitamins, and they may manifest clinical evidence of avitaminosis For example, we often see symptoms such as diarrhea, with or without definite skin lesions about the mouth or hands and mild confusional states which clear up with the administration of nicotinic acid, usually 100 mg twice a day. Thiamine chloride is given routinely in all cases, 10 mg a day Brewers' yeast is given usually in powdered form, ½ ounce twice a day The diet of patients is also high in vitamin content They all receive fruit juices of one sort or another, and the diet is balanced with regard to fat, protein, and carbohydrate content as well.

In addition, we give infusions of glucose in saline to combat dehydration, since these patients may lose a lot of fluid through vomiting, sweating, and diarrhea Infusions of glucose are given as often as twice a day, and the patients seem to obtain a great deal of relief Just why relief from the abstinence symptoms, especially aching of the muscles, is obtained from infusions of glucose is not clear, because there is actually a rise of blood sugar during withdrawal There is no restriction of any therapeutic measures which the doctor may deem indicated, but we do not use any of the so called "specific' drugs, such as hyoscine or belladonna

While still on the admission service the patient is studied from a psychosomatic point of view A thorough physical examination is made as soon as possible after admission There are a few diseases which are contraindications to rapid withdrawal Withdrawal of morphine is not begun immediately in patients with cardiac failure, active tuberculosis,

pneumonia or other infectious diseases They are sent to the medical or the surgical service and are maintained on stabilization doses of morphine until their condition has been cured or improved sufficiently to permit withdrawal, which is carried out on the admission service In such cases withdrawal may be slow, taking a month or more Patients with tuberculosis do better when they are not taking morphine, but if the disease process is far advanced and active, withdrawal is not usually attempted Pain associated with inoperable cancer is a contraindication to withdrawal Tabetic crises are very difficult to handle It is hard to evaluate the severity of the pain suffered by these patients, but an attempt is made to do so on the basis of the neurologic findings During the crisis no attempt is made to withhold morphine, but, after reduction is achieved, pain due to crises is treated with paraldehyde, Avertin, or other nonopiate hypnotics, and analgesics Between crises, the patient s syphilitic condition is treated as it would be in nonaddict patients

As soon as the patient s physical condition permits, psychiatric and psychometric examinations are made On the basis of these and reports from the social service department concerning the patient s history as well as reports from other sources the patient is classified from the standpoint of personality and prognosis This forms the basis for treatment of the third aspect of addiction, habituation

The classification in use at Lexington was devised by Dr Kolb and includes 6 groups The first consists of normal persons who have become addicted accidentally or necessarily in the treatment of an illness In the second group are those with so-called ' psychopathic diatheses The third includes those with frank psychoneuroses The fourth comprises psychopathic personalities The fifth is the inebriate group, and the sixth consists of patients with psychoses This classification was made from a practical point of view because addicts must be divided and somewhat segregated so that further treat

ment of the basic underlying personality defects may be more effective We try to select those cases which can benefit from psychiatric treatment From this standpoint this classification has proved to be very valuable

The first group, made up of those accidentally addicted, is very small In two and one half years at Lexington no case of this sort came under my personal observation Dr Pescor cites a figure of 3 8 per cent based on a study of several hundred records However, opinions as to the normality of individuals vary from doctor to doctor, and some bias in one or the other direction undoubtedly exists The low percentage of "normal individuals in the Lexington hospital does not mean that only abnormal persons are addicted to morphine It means merely that we do not often get patients of the first group Many persons with chronic illnesses—cardiac disease, for example—may become addicted to morphine because of treatment of their basic illness, but withdrawal of morphine alone suffices for cure They go through the withdrawal stage and the abstinence syndrome, do not relapse, and consequently have no need to come to a special institution for treatment The fact that we do not see many such cases does not mean that they are rare

The second group, made up of those with psychopathic diatheses, is not a clean cut group with well crystallized personalities These patients are maladjusted individuals who do not fit into other classifications The basic mechanisms underlying their behavior may be neurotic, thus, they may be compulsive, obsessive, anxious, or neurasthenic in a general way, but not enough to give rise to specific symptoms which can be termed psychoneurotic The term "character neuroses' has been applied to such personalities In Dr. Kolb s original description of these types, emphasis was laid upon the hedonistic, carefree, pleasure seeking type of individual In practice many of these are included in the fourth or psychopathic group Persons who would be placed in the "psychopathic diathesis" group at Lexington are very common in the general

population. They do not get into much trouble and their legal offenses are generally limited to violation of the narcotics act. They are not habitual criminals.

The third or psychoneurotic group are those with definite neuroses which do not differ from those seen in nonaddicts. Addiction to morphine in these cases is usually secondary to the psychoneurosis. Anxiety types are perhaps the most common.

In the fourth group are the well-crystallized psychopathic personalities. Some have an extensive criminal background, not necessarily restricted to violation of the narcotics act. Their personal histories are almost monotonously alike. The patient is usually born in a home which is submarginal economically, broken up by death, divorce, or separation of parents. His troubles begin in grammar school. He is arrested by the truant officer, runs away from home or "reform school," and is involved in various forms of juvenile delinquency. There are rapid changes of work, which usually is sporadic and interspersed with illegal activities, such as swindling, shortchanging, "confidence games," bookmaking, and gambling. However, these persons manage to stay out of the clutches of the law most of the time. Alcoholism, vagabondage, and homosexuality are quite common. Most of such patients will not be cured by any method, but their presence in an institution at least serves to keep them away from drugs for a while and to protect the public.

The fifth group consists of periodic inebriates—the spree-drinkers who have become addicted to morphine through alcohol. *They usually take the drug for relief from alcoholic* hangovers and then begin to prefer the drug alone. After a "cure," they relapse to spree-drinking, again take morphine for hangovers, and find themselves addicted to morphine once more. This group is not a homogeneous one, but the common problem of spree-drinking makes it expedient to place them in a single category.

Psychoses due to opiates or opiate addiction per se are said to exist, but no such case has ever been seen at Lexington. Psychotic patients with active "habits" are admitted, but their psychoses antedate or are unrelated to addiction. Of these cases, paranoid schizophrenia probably constitutes the largest single group.

After the patient is in condition to do so he is brought before a classification board, where all the facts I have mentioned are considered, and the patient is assigned to a suitable department of the institution for further treatment. He may be recommended for special psychotherapy or may be treated routinely. He is assigned to a definite occupation on the farm, in the industries, maintenance shops, or hospital, and he is given vocational training if necessary. In the time available, which we think must be at least 6 months in the average case, an attempt is made to correct, as far as possible, basic personality difficulties which predispose the patient to relapse. Each patient is assigned to a psychiatrist who administers psychotherapy as indicated and who interviews all patients under his care from time to time to follow their progress. The patient's general health is cared for by daily clinics, or "sick calls," as they are termed, and the facilities of a complete general hospital within the institution are available to him at all times. He may also avail himself of diversified educational and recreational facilities. After a period of about 6 months the patient is considered for discharge by the medical staff, provided this is consonant with the sentence, if any, which he has to serve. The criterion for discharge as cured is whether or not the patient has acquired the power for self-control with reference to the use of narcotic, habit-forming drugs as defined by law. If discharge is recommended, efforts at occupational placement and follow-up studies are made by the social service department.

This, in a general way, suffices for a d [illegible] f the treatment of drug addicts at the U.S. Publi [illegible] ice Ho

pital at Lexington, Kentucky. Now we can take up any special aspects of the problem which you may wish to inquire about.

Dr. Wolff: I wonder if you could tell us the percentage of cures in the various groups.

Dr. Wikler: The percentage of cures has not been broken down with respect to each of the groups in Dr. Kolb's classification. In general it is difficult to state when a patient is actually cured. We call a patient "cured" when he not only is not physically dependent upon drugs but does not relapse to the use of them. Because of legal complications and other administrative difficulties, our follow-up system is not wholly satisfactory, but a very conservative estimate is that about 12 per cent of the patients that are treated are actually cured. There is a large group of patients whom we lose track of after they leave the institution; it is reasonable to assume that a considerable percentage of these remain "cured." However, 35 per cent of those treated are known definitely to relapse. As for the 12 per cent that are actually cured, I know of no study regarding their distribution in the Kolb classification. From my own personal experience I would say that our cures are obtained chiefly from the second group and the occasional patient in the first group.

Dr. Harry Gold: The so-called cure—that is, having the patient leave the hospital without symptoms and without drug—applies to 100 per cent of those cases, does it not?

Dr. Wikler: We do not call that a cure. If the patient leaves the hospital he obviously has been cured in the sense that he is no longer physically dependent upon the drug, but if he relapses as soon as he steps outside the gate, we cannot consider that he has been cured.

Dr. Gold: That takes how long on the average?

Dr. Wikler: We feel that about 6 months is required. Studies on the physical condition of those patients with respect to the effects of the drug seem to indicate that after the withdrawal of opiates the patient is not free from the effects of ad-

if their addiction is mild Furthermore, the symptoms and signs observed in addicted animals, such as the dog, the mon key, and especially the chimpanzee, are similar to those seen in human beings The progression of these symptoms is also almost identical Moreover, the failure of hypnosis barbitu rates, and the lowering of body temperature to influence the abstinence signs significantly suggest that they are not merely the manifestations of experienced anxiety or terror

Dr McKeen Cattell Do you have any criteria for determin ing which of the withdrawal symptoms are entirely psycho logic?

Dr Wikler No, it is impossible to say which particular ab stinence sign is psychologic and which is not

Dr Wolff I notice that you build up the patients after with drawal Is there any advantage in building them up and then withdrawing?

Dr Wikler If the patient's condition is very poor we try to build him up first and then withdraw, but in the average case we do not believe that there is much to be gained by build ing the patient up from a marginal level to a very good one before withdrawing

Dr Wolff I understand there are important fluctuations in the weight curve before and after withdrawal Will you comment on that?

Dr Wikler During the period of abstinence there is quite a drop in the curve, which gradually rises again after with drawal is completed

Dr Wolff Is there an average drop of about 3 Kg ?

Dr Wikler About that 3 or 4 Kg during withdrawal

Dr Wolff Is the patient eating well during that period?

Dr Wikler The curves of weight and caloric intake are in general parallel during the first 5 days after withdrawal Later they diverge

Dr Wolff Is there a period of hydration during which the patients gain weight from the fluid intake?

Dr Wikler Yes Addiction is accompanied by hydration, as studies by Dr Williams have shown

Dr Gold I take it, from all that you have said, that physical dependence is of little importance in the larger problem of controlling morphine addiction The symptoms of physical dependence may be cured in 10 days or so Psychic dependence or habituation seems to be the aspect of addiction so resistant to cure Do you agree?

Dr Wikler Most important is the role of personality in the development of addiction That question has been discussed by many people There is no general agreement, but it appears to many observers, and Drs Kolb and Himmelsbach have so stated, that the basic problem is one of personality defect People who have so-called inadequate personalities find it more difficult to discontinue the use of the drug once physical dependence has been established, because of the discomfort attending withdrawal They therefore continue to use it even when they no longer obtain the "lift" or feeling of euphoria for which they took it in the first place The economic, social, and personal consequences are disastrous For these reasons the development of physical dependence must be considered an important phase of the problem of drug addiction

Intern What is your attitude toward the use of insulin in these cases?

Dr Wikler I have had no experience with that personally, but Drs Kolb and Himmelsbach state that it is of no value in the treatment of withdrawal symptoms We sometimes use insulin in 15 unit doses several times a day to improve appetite and promote the ingestion of food during the period of fall in the caloric intake curve We find that that is of some value in maintaining the weight of the patient during withdrawal

Dr Cattell Have you had any experience with marihuana in relation to morphine addiction?

[EDITOR The essentials of this conference are applicable today even though several years have elapsed since it was held The few changes that have taken place were supplied by Dr Wikler Application forms for voluntary admission to the U S Public Health Service Hospital at Lexington, Ky, may be obtained from the medical officer in charge at that institution

In recent years, methadone, a potent synthetic analgesic agent has been used in treating active opiate addiction It is the current practice to use 1 mg of methadone in the place of 3 mg of morphine After stabilization takes place, the methadone is discontinued by a method of rapid reduction The discomforts in this system for withdrawal of narcotics, although more prolonged, are milder than by the plan described in the conference

Among other measures, insulin has proved to be without value in controlling the physical dependence of opiate addiction Recent work shows that hydration probably plays no part in causing the morphine abstinence syndrome There are the observations that experimental hydration in man fails to produce symptoms resembling morphine abstinence, that they fail to appear during the diuresis after the hydration is terminated, and that the hydration noted during addiction in man is due to secondary anemia Bilateral frontal lobotomy, in man, markedly reduces the craving and goal directed activity related to obtaining narcotics shown by addicted patients after abrupt withdrawal of morphine

The recent literature on the clinical aspects of addiction to opiates is reviewed by Isbell and Fraser in *Pharmacological Reviews*, August, 1950 In the same journal, December, 1950, problems relating to the sites and mechanisms of action of morphine and related drugs in the central nervous system are discussed by Wikler]

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